An open-label, balanced, randomized, two-treatment, two-period, two sequence, single dose, two-way crossover, bioequivalence study of Lamotrigine 50 mg tablets in healthy, adult, human subjects under fed conditions

Dissertation submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

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In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACOLOGY

BY

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This is to certify that the dissertation entitled **"An open-label, balanced, randomized, two-treatment, two-period, two sequence, single-dose, two-way crossover, bioequivalence study of Lamotrigine 50 mg tablets in healthy, adult, human subjects under fed conditions"** submitted to The Tamilnadu Dr. M.G.R. Medical university, Chennai, in partial fulfillment for the award of degree of **Master of Pharmacy in Pharmacology** is a bonafide individual research work done by **V.Saravanan (Reg.No.261226013),** Mohamed Sathak A.J.College of Pharmacy, Chennai, under the guidance and direct supervision of **Malini Sen M.Pharm, Assistant Professor, Department of Pharmacology** during the academic year 2013-2014.

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DECLARATION OF THE CANDIDATE

I hereby declare that the thesis titled **"An open-label, balanced, randomized, two-treatment, two-period, two sequence, single-dose, two-way crossover, bioequivalence study of Lamotrigine 50 mg tablets in healthy, adult, human subjects under fed conditions"** submitted in partial fulfillment for the award of degree Master of Pharmacy to The Tamilnadu Dr. M.G.R. Medical University and carried out at Mohamed Sathak A.J.College of Pharmacy, Chennai, is my original and independent work done under the direct supervision and guidance of **Malini Sen M.Pharm, Assistant Professor, Department of Pharmacology** during the academic year 2013-2014 and this thesis contains no material which has been accepted for the award of any degree or diploma of other Universities.

Place: Chennai

Date: **[V.Saravanan]**

Dedicated to my

Parents, Teachers

&

Friends

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{V.SARAVANAN]

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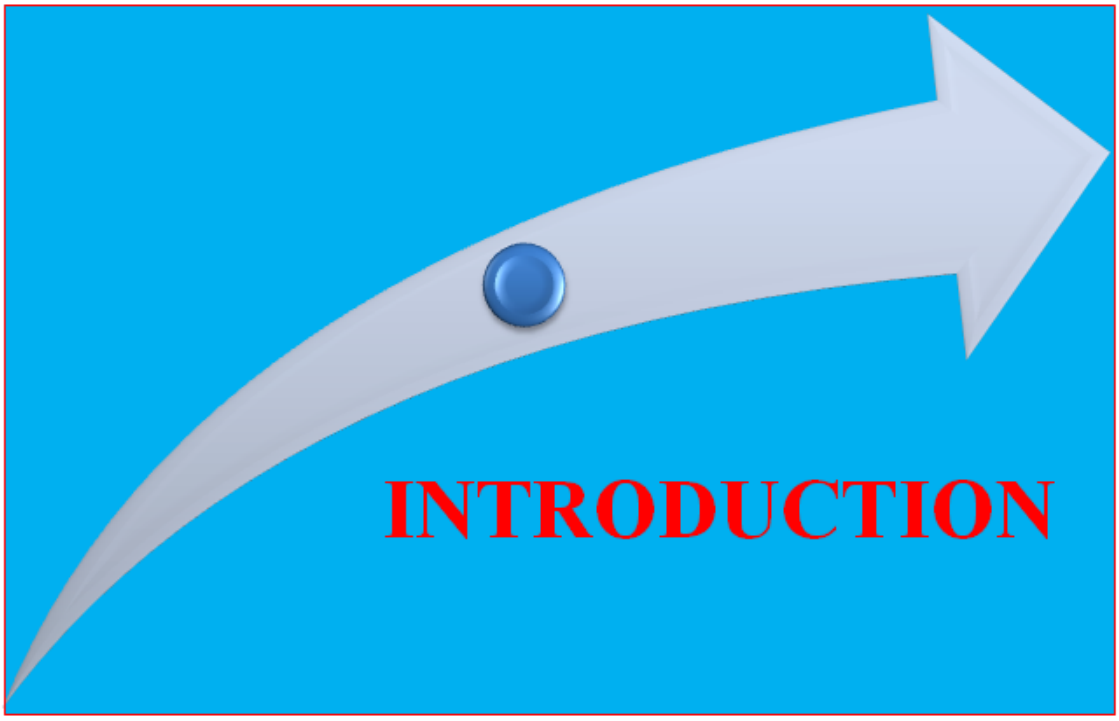
LISTS OF TABLES & FIGURES

LIST OF ABBREVIATIONS

AE	:	Adverse Event
ANOVA	:	Analysis of Variance
AUC	:	Area Under the Curve
°C	:	Degree Celsius
BA	:	Bioavailability
BE	:	Bioequivalence
BMI	:	Body Mass Index
CRF	:	Case Report Form
Cm	:	Centimeter
C_{max}	:	Peak Plasma Concentration
GCP	:	Good Clinical Practice
GLP	:	Good Laboratory Practice
g / dL (or) gm / dL	:	Gram per Decilitre
hrs	:	Hour(s)

ICH	:	International Conference on Harmonization
IEC	:	Independent Ethics Committee
ICD	:	Informed Consent Document
ICMR	:	Indian Council of Medical Research
Inc.	:	Incorporation
i.v.	:	Intravenous
IU / L	:	International unit per Litre
Kg	:	Kilogram
Kg/m^2	:	Kilogram per Meter Square
K_2EDTA	:	Dipotassium Ethylene Diamine Tetra Acetic Acid
L / Cumm	:	Lakhs per Cubic Millimeter
Max	:	Maximum
MEC	:	Minimum effective concentration
mg	:	Milligram
min	:	Minute
Min	:	Minimum
mL	:	Milliliter
MSC	:	Maximum safe concentration
NA	:	Not Available

No.	:	Number
N	:	Number of Subjects
P	:	Period
Pvt Ltd	:	Private Limited
QA	:	Quality Assurance
RPM	:	Revolution Per Minute
SAS	:	Statistical Analysis software
SD	:	Standard Deviation
SOP	:	Standard Operating Procedure
t_{max}	:	Time to reach peak plasma concentration
$t_{1/2}$	:	Terminal Elimination half-life
X-RAY	:	Roentgenogram
Yrs	:	Years


INTRODUCTION

1. INTRODUCTION

In pharmacology, bioavailability (BA) is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reaches the systemic circulation, which is one of the principal pharmacokinetic properties of drug. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as oral), its bioavailability generally decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient. Bioavailability is one of the essential tools in pharmacokinetics as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

Bioequivalence (BE) study is a comparative study of bioavailability among drug products that contain the same active agents. Bioavailability and bioequivalence of drug products and drug product selection have emerged as critical issues in pharmacy and medicine during the last three decades. Concern about lowering health costs resulted in tremendous written increase in the use of generic drug products. Currently about one half of all prescriptions written are for drugs that can be substituted with a generic drug.

This circumstantial growth of generic pharmaceutical industry and the abundance of multisource products have prompted some questions among health professionals and scientists regarding the therapeutic equivalency of these products. Inherent in the currently accepted guidelines for product substitution is the assumption that a generic drug considered to be equivalent to a innovator drug would elicit the same clinical effect. Numerous papers in the literature indicate that there is concern that the current standards for approval of generic drugs may not always ensure therapeutic equivalence. The availability of different formulations of the same drug substance given at the same strength and in the same dosage form poses a special challenge to health care professionals.

1.1 Bioavailability [1]

Bioavailability is defined as: “The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the systemic circulation.”

Bioavailability:

- It is the fraction of unchanged drug reaching the systemic circulation following administration by any route.
- To exert an optimal therapeutic action, an active moiety should be delivered to its site of action in an effective concentration for the desired period.
- The influence of route of administration on drug's bioavailability is:
  Parenteral > oral > rectal > topical
- Intravenous injection of a drug results in 100% bioavailability as the absorption process is bypassed. Even in such cases, the dose available to the patient called as the bioavailable dose is often less than the administered dose.
- Estimation of bioavailability is a means of predicting the clinical efficacy of a drug.
- Bioavailability testing measuring the rate and extent of drug absorption is a way to obtain evidence of the therapeutic utility of a drug product.

Fraction of administered dose that enters the systemic circulation

$$F = \frac{\text{Bioavailable dose}}{\text{Administered dose}}$$

It ranges from 0 to 1. Bioavailability is normally expressed as %.

1.1.1 Types of Bioavailability

Absolute bioavailability (F)

- When systemic availability of drug administered orally is determined in comparison to it's intravenous administration ie is called absolute bioavailability.
- It's determination is used to characterize a drug's inherent absorption properties from the extra vascular site.

$$\text{Absolute bioavailability} = \frac{[AUC]ev/(Dose)ev}{[AUC]iv/(Dose)iv}$$

(ev- extra vascular, iv- intravenous and AUC – Area Under the Curve)

Relative Bioavailability (Fr)

- When systemic availability of drug after oral administration is compared with that of an oral standard of same drug (such as an aqueous or non-aqueous solution or suspension), it is referred as relative bioavailability.
- It is used to characterize absorption of drug from its formulation.

$$\text{Relative Bioavailability} = \frac{[AUC]test\ /(Dose)test}{[AUC]std/(Dose)std}$$

- Before the therapeutic effect of an orally administered drug can be realized, the drug must be absorbed.

Supra bioavailability

Supra bioavailability is a term used when a test product displays larger bioavailability than the reference product. Such formulations are usually not to be accepted as therapeutically equivalent to the existing reference product.

1.1.2 General Objectives of Bioavailability Studies[2]

Bioavailability studies are important in the determination of influence of excipients, patient related factors, and possible interaction with other drugs on the efficiency of absorption.

- Development of new formulations of the existing drugs e.g. innovator vs generic. Bioequivalence study looking for similarity of F and ka values between the products.
- To compare one type of dosage form with another e.g. tablet versus intravenous dosage form or regular tablet with sustained release tablet. Bioavailability study where ka and F are to be determined. Changes in ka may be intentional (slow release) whereas F values should be similar.

Factors Influencing Bioavailability

The absolute bioavailability of a drug when administered by an extra vascular route is usually less than one (i.e. $F<1$). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation.[8]

Such factors may include but are not limited to:

- Physical properties of the drug (hydrophobicity, pKa, and solubility)
- The drug formulation (immediate release, excipients used, manufacturing methods, modified release - delayed release, extended release, and sustained release, etc.)
- If the drug is administered in a fed or fasted state
- Gastric emptying rate
- Circadian differences
- Enzyme induction/inhibition by other drugs/foods.
- Disease state e.g. Hepatic insufficiency, poor renal function

Each of these factors may vary from patient to patient (inter-individual variation) and indeed in the same patient over time (intra-individual variation). Whether a drug is taken with or without food will affect absorption. Other drugs taken concurrently may alter absorption and first-pass metabolism. Intestinal motility alters the dissolution of the drug and may affect the degree of chemical degradation of the drug by intestinal micro flora. Disease states affecting liver metabolism or gastrointestinal function will also have an effect.

Absolute bioavailability compares the bioavailability (estimated as area under the curve, or AUC) of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration) with the bioavailability of the same drug following intravenous administration.

Relative bioavailability is extremely sensitive to drug formulation. Relative bioavailability is one of the measures used to assess bioequivalence between two drug products as it is the Test/ Reference ratio of AUC. The maximum concentration of drug in plasma or serum (C_{max}) is also usually used to assess the bioequivalence.

If the size of the dose to be administered is same, then bioavailability of a drug from its dosage form depends upon three major factors:

- Pharmaceutical factors related to physiochemical properties of the drug and characteristics of dosage form.
- Patient related factors.
- Route of administration.

1.1.3 Methods for assessing bioavailability[2]

The methods useful in quantitative evaluation can be divided into 2 categories

I. Pharmacokinetic methods (indirect method)

These are very widely used and based on the assumption that the pharmacokinetic profile reflects the therapeutic effectiveness of a drug. Thus, these are indirect methods**.**

There are two methods in this type:

1. Plasma level-time studies
2. Urinary excretion studies

II. Pharmacodynamic methods (direct method)

These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on pathophysiological process as a function of time.

The two pharmacodynamic methods are:

1. Acute pharmacological response
2. Therapeutic response

Pharmacokinetic Parameters[3]

C_{max}: Maximum measured plasma concentration after the administration of single dose of the drug expressed in terms of μg/mL or ng/mL.

AUC_{0-t}: The area under the plasma concentration versus time curve from time zero to the last time point with measurable concentration calculated by the linear trapezoidal method.

$AUC_{0-\infty}$: The area under the plasma concentration versus time curve from time zero to time infinity. $AUC_{0-\infty}$ is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant.

T_{max}: Time of maximum measured plasma concentration. If the maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period, which is an indication of the rate of absorption expressed in terms of hours or minutes.

K_{el}: Apparent first order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve.

$T_{1/2}$: Apparent first-order terminal elimination half-life will be calculated as $0.0693/K_{el.}$ The various pharmacodynamic parameters, which influence the above mentioned pharmacokinetic parameters are:

Minimum Effective Concentration (MEC) [3]

It is defined as the minimum concentration of drug in plasma required to produce the therapeutic effect. It reflects the minimum concentration of the drug at the receptor site to elicit the desired pharmacologic response. The concentration of drug below MEC is said to be in the sub therapeutic level.

Maximum Safe Concentration (MSC) [3]

Also called as minimum toxic concentration, it is the concentration of the drug in plasma above which adverse or unwanted effects are precipitated. Concentration of drug above MSC is said to be in the toxic level.

Onset of Action

The interval between the beginning of pharmacologic response and drug administration is called as onset of action. It occurs when the plasma drug concentration exceeds the required MEC.

Onset Time

It is the time required for the drug to start producing pharmacologic response. It corresponds to the time of plasma concentration to reach MEC after administration of drug.

Duration of Action

The time period for which the plasma concentration of drug remains above the MEC level is called as duration of drug action.

Therapeutic Range

The drug concentration between MEC and MSC represents the therapeutic range.

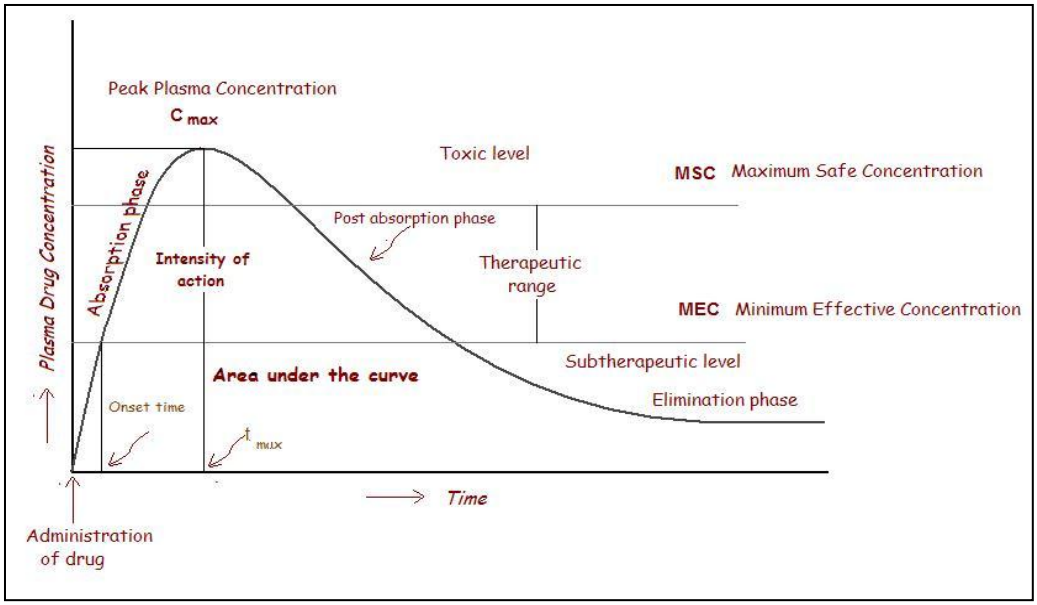


Figure 1: Pharmacokinetic parameters.

Bioavailability is needed for

- Drugs having low therapeutic index e.g. cardiac glycosides, quinidine, phenytoin etc.
- The peak levels of drugs are required to find the effect of drugs e.g. phenytoin, phenobarbitone, primidone, sodium valproate, anti-hypertensives, antidiabetics and antibiotics.
- Drugs that are absorbed by an active transport e.g. amino acid analogues, purine analogues etc.
- Drugs which are disintegrated in the alimentary canal and liver e.g. chlorpromazine etc., or those which under go first pass metabolism.
- Formulations that give sustained release of drug with smaller disintegration time than dissolution rate and drugs used as replacement therapy also warrant bioavailability testing. In addition, any new formulation has to be tested for its bioavailability profile.

1.2 Bioequivalence (BE) [3]

Chemical equivalents, which when administered to the same individuals in the same dosage regimen will result in comparable bioavailability. Bioequivalence gained increasing attention during the last 40 years after it became evident that marketed products having the same amounts of the drug may exhibit marked differences in their therapeutic responses. When drug products are administered to individuals, the investigator inevitably finds differences in one or more of the variables measured. These differences are due partly to factors related to dosage form and partly to biological factors unique to each individual since each person has his own characteristics for absorption, metabolism, and excretion of each drug. Through appropriate use of statistical procedures, it is possible to identify the variations that result from differences among individuals and thus to isolate those that result from differences in the bioavailability of the drug products. Generally, these differences were well correlated to dissimilar drug plasma levels caused mainly by impaired absorption. Now a considerable body of evidence has accumulated indicating that drug response is better correlated with the plasma concentration or with the amount of drug in the body than with the dose administered. Consequently, on the basis of simple pharmacokinetic concepts and parameters, bioavailability and bioequivalence studies have been established as acceptable surrogates for expensive complicated and lengthy clinical trials and are used extensively worldwide to establish and ensure consistent quality and a reliable therapeutically effective performance of marketed dosage forms.

Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the innovator (reference) product on the basis that if two formulations exhibit similar drug concentration-time profiles in the blood/plasma, they should exhibit similar therapeutic effects.

Three situations have thus been defined in which bioequivalence studies are required:

- When the proposed marketed dosage form is different from that used in pivotal clinical trials.
- When significant changes are made during the manufacturing of the marketed formulation.
- When a new generic formulation is tested against the innovator's marketed product.

Comparative evidence may require not only studies in a fasting condition but following a specified meal. The latter permit drug formulations to be evaluated under "stressed conditions". If it is shown that competitive products are bioequivalent under both fasting and fed conditions, there is greater confidence that they are therapeutically equivalent when used in patients. Bio-equivalent simply means a drug or dosage form of a drug or supplement is equivalent to a reference brand or dosage form of the same drug or supplement in terms of various bioavailability parameters measured via *in-vivo* testing in human subject.

1.2.1 Factors Influencing Bioequivalence[4]

- Delayed gastric emptying
- Stimulation of bile flow
- Change in gastrointestinal pH
- Increase splanchnic blood flow
- Change in luminal metabolism of a drug substance
- Physical or chemical interaction with a dosage form or a drug substance
- Food can change the BA of a drug and hence can influence the BE between test and reference products

1.2.2 Types of bioequivalence[4]

Chemical equivalence

It indicates that two or more drug products that contain the same chemical substance as an active ingredient in the same amount.

Pharmaceutical equivalence

It is a relative term, which denotes that the drug substance in two or more forms is identical in strength, quality, purity, content uniformity, disintegration and dissolution characteristics. They may however differ in containing different excipients.

Therapeutic equivalence

It indicates that two or more drug products that contain the same therapeutically active ingredient elicits identical pharmacological effects and can control the disease to the same extent.

Types of bioequivalence studies

- *In vivo* studies
- *In vitro* studies

In Vivo Studies

The following points are used in assessing the need for in vivo studies:

- Oral immediate release products with systemic action.
  - Indicated for serious conditions requiring assured response.
  - Narrow therapeutic margin.
  - Pharmacokinetics complicated by absorption lesser than 70% or non linear kinetics, presystemic elimination greater than 70%.
  - Unfavorable physiochemical properties like low solubility, metastable conditions, instability,etc.
- Non- oral immediate release products.
- Modified release products with systemic action.

In Vitro Studies

If none of the above criteria is applicable, comparative in vitro dissolution studies will suffice. In vitro studies are conducted in cases where,

- The product is intended for topical administration (Cream, ointment, and gel) for local effect.
- The product is for oral administration but not intended to be absorbed (antacid or opaque medium).
- The product is administered by inhalation as a gas or vapour.

1.3 General Concepts of Design and Conduct of Studies[5]

The design and conduct of the study should follow the Good Clinical Practice including reference to an Ethics Committee.

As recommended by the US FDA (1992), in most bioequivalence trials, a test formulation is compared with the standard/innovator reference formulation in a group of normal healthy subjects (18-45 year) each of whom receive both the treatments alternately in a crossover fashion (two-period, two-treatment crossover design) with the two phases of treatment separated by a washout period of generally a week duration but may be longer (a minimum time equivalent to 5 half-lives) if the elimination half-life of the drug is very long. The treatment is assigned to each subject randomly but an equal number of subjects receive each treatment in each phase. Thus in case of two treatments standard (S) and test (T), one group gets the treatment in the order S and T and the second group in the reverse order T and S. This is done to avoid the occurrence of possible sequence or period effects. A similar allocation is done in case of a three-treatment crossover design (three-period, three-treatment crossover design).

For several drugs, a great inter-subject variability in clearance is observed. The intra-subject coefficient of variation (approximately 15%) is usually substantially smaller than that between subjects (approximately 30%) and therefore, crossover designs are generally recommended for bioequivalence studies.

The primary advantage of the crossover design is that since the treatments are compared on the same subject, the inter subject variability does not contribute to the error variability. If the drug under investigation and/or its metabolites has an extremely long half-life, a parallel group design may be indicated. In a parallel group design, subjects are divided randomly into groups and each group receive one treatment only. Thus each subject receives only one treatment. In a parallel design, although one does not have to worry about sequence period or carry over effects or dropouts during the study. The inter-subject variability being very high, the sensitivity of the test is considerably reduced thus requiring a larger number of subjects compared to a crossover design to attain the same sensitivity.

Inherent in both the crossover and parallel designs are the three fundamental statistical concepts of study design namely

- Randomization
- Replication and Error control.

Randomization

It implies allocation of treatments to the subjects without selection bias. Consequently randomization is essential to determine an unbiased estimate of the treatment effects.

Replication

It implies that a treatment is applied to more than one experimental unit (subject) to obtain more reliable estimates than is possible from a single observation and hence provides a more precise measurement of treatment effects. The number of replicates (sample size) required will depend upon the degree of differences to be detected and inherent variability of the data. Replication is used concomitantly with Error control to reduce the experimental error or error variability.

More commonly used replicated crossover designs to compare two formulations are:

- Four-sequence and two-period design (Balaam's design)
- Two-sequence and four-period design
- Four-sequence and four-period design
- Two-sequence and three-period design
- Crossover design for three medications (Williams's design)
- Crossover design for four medications (Williams's design)
- Crossover design for two medications (t - test; r - reference)

2x2 Crossover design [6]

This is a conventional not-replicated design with two formulations, two periods, two sequences that may be represented as follows:

Sequence	Period 1	Period 2
1	R	T
2	T	R

Each individual is randomly assigned to RT or TR sequence in two dosage periods. That is, individuals assigned to RT (TR) sequence receive formulation R in the first dosage period and formulation T in the second dosage period. Randomization for a 2x2 crossover study may be carried out through tables of random numbers or randomization procedures implemented by statistical software.

Replicated crossover design[6]

This design is recommended for bioequivalence studies of formulations with modified-release dosage or highly variable products (intra-individual variation coefficient ≥30%), including the quick-release, and modified-release ones and other oral administration products.

The same test and reference formulation batches shall be used for this design for replicated administration. The periods shall be sufficiently spaced (washout) to assure non-existence of carryover effects.

Four-sequence and two-period design (Balaam's design)

In this design, test (T) and reference (R) will be taken in two period and four sequence pattern in order to compare two formulations of a drug.

Sequence	Period 1	Period 2
1	T	T
2	R	R
3	R	T
4	T	R

Two-sequence and four-period design

In this design, there will be four periods and two sequences. To know the typical drug concentration variations in human subjects regarding test and references, number of periods can be increased.

	Period			
Sequence	1	2	3	4
1	T	R	R	T
2	R	T	T	R

Four-sequence and four-period design

Here the design consists of four periods and four sequences. It is a most typical replicated crossover design.

	Period			
Sequence	1	2	3	4
1	T	T	R	R
2	R	R	T	T
3	T	R	R	T
4	R	T	T	R

Two-sequence and three-period design

In this design, subjects will undergo three period and two sequence design.

	Period		
Sequence	1	2	3
1	T	R	T
2	R	T	R

Crossover design for three medications (William's design)

(William's design with T1 = test 1, T2 = test 2, R = reference)

In order to compare three formulations of a drug, there are a total of three possible comparison pairs among formulations: formulation 1 versus formulation 2, formulation 1 versus formulation 3, and formulation 2 versus formulation 3.

	Period		
Sequence	1	2	3
1	R	T2	T1
2	T1	R	T2
3	T2	T1	R
4	T1	T2	R
5	T2	R	T1
6	R	T1	T2

1.3.1 Types of BA/BE Studies[7]

Fasting Study

After an overnight fast of at least 10 hrs, subjects are made to continue t**o** fast for up to 4 hours after dosing.

Fed Study

After an overnight fast of at least 10 hrs, subjects are given a high calorie-high fat breakfast 60 minute prior to administration of the drug product.

1.3.2 Quality Control and Quality Assurance[8]

Quality Control:

The principal investigator by careful planning, assigning responsibilities to well qualified study personnel, through continuous review, verifies and maintains desired level of quality in the study.

Quality Assurance:

Review will be carried out by the QA department to confirm that deviations if any from approved protocol or SOP are adequately documented.

1.3.3 Ethical Considerations[8]

Basic Principles

The study will be carried out in accordance with the provisions of current versions of ICH guidance for Good Clinical Practices and ICMR guidance for biomedical research on human subjects.

Ethics Committees

The protocol and informed consent will be submitted to the IRB/IEC for review. Upon approval, the study will be conducted as per the approved protocol.

Informed Consent Form

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. A reference copy of the form shall be given to the respective subjects.

Termination of Study

The sponsor reserves the right to discontinue the study at any time, upon IRB approval. Reasons for the termination will be provided to the subjects and IRB. The investigator reserves the right to discontinue the study at any time for the reasons of subject safety and welfare. The Ethics Committee may terminate the study, if there are major violations of ethics or due to any serious adverse effects.

Subject Compensation

The subjects will be paid an adequate compensation by the Ethics Committee on account of their time participation in the trail and for any inconvenience caused. In case of discontinuation from study before completion of study, the compensation will be paid according to the compensation policy.

Insurance Policy

The study will be covered by an insurance contract, wherein all subjects participating in any study is covered for indemnity and medical expenses.

Drawing and Disposal of Plasma Samples

The plasma samples should be drawn only when a proper validated bio analytical method is available and disposed after submission of study report.


REVIEW OF
LITERATURE

2. REVIEW OF LITERATURE

Lamotrigine is a phenyltriazine used in the treatment of epilepsy and bipolar disorder type I. Following are the literature review results retrieved for the clinical studies and meta-analysis carried out on lamotrigine.

In 2012, Ruiz et al, stated that the test and reference products of lamotrigine 100 mg tablets complied with the regulatory criteria for equivalence with respect to rate and extent of absorption according to the guidances of Instituto Nacional de Vigilancia de Medicamentos y Alimentos and FDA through a single-dose, two treatment, two-period, two-sequence crossover study in healthy Thai male volunteers.[9]

In 2012, Perez-Lloret S et al, stated that the test and reference products lamotrigine 50 mg tablets met the regulatory criteria for bioequivalence and suggested that bioequivalence studies evaluating 50-mg doses of Lamotrigine are feasible and recommended, since such doses may minimize the risk of severe rash or Stevens-Johnson Syndrome through the a randomized, single-dose, 2-period, 2-sequence crossover study in fasting healthy volunteers.[10]

In 2008, Srichaiya A et al, stated that test and reference product of lamotrigine 100-mg tablets were bioequivalent in the healthy Thai male subjects, based on the US FDA's regulatory definition through a randomized, single-dose, two-period, two-sequence crossover study.[11]

In 2007, Makus KG et al, stated that some patients may experience loss of seizure control when generic lamotrigine is substituted for the branded formulation through a case-series analysis of Health Canada adverse-reaction forms submitted to pharmacists by physicians were retrieved, and from a physician chart audit and survey.[12]

In 2012, Hartung DM et al, stated that a statistically significant increase in emergency visits, hospitalizations or condition-specific encounters was not observed following the switch from brand to generic lamotrigine, although a type II error cannot be ruled out through a retrospective cohort-crossover design using state Medicaid claims data from July 2006 through June 2009.[13]

In 2008, Calabrese JR et al, stated that lamotrigine 200 mg/day demonstrated significant antidepressant efficacy on the 17-item HAM-D, HAM-D Item 1, MADRS, CGI-S, and CGI-I compared with placebo through a double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression.[14]

In 2004, McElroy SL et al, stated that bipolar I patients experienced sustained improvement in depressive symptoms without evidence of mood destabilization through A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression.[15]

In 2006, Brown EB et al, stated that patients with acute bipolar I depression had statistically significantly greater improvement in depressive and manic symptoms, more treatment-emergent adverse events, greater weight gain, and some elevated metabolic factors with olanzapine/fluoxetine than lamotrigine through a 7-week, randomized, double-blind trial.[16]

In 2000, Calabrese JR et al, indicated that lamotrigine monotherapy is a useful treatment for some patients with rapid-cycling bipolar disorder through a double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder.[17]

In 2003, Barbosa L et al, stated potential efficacy of the antidepressant profile of lamotrigine and possible role of lamotrigine as an augmentation agent in depression through a double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes.[18]

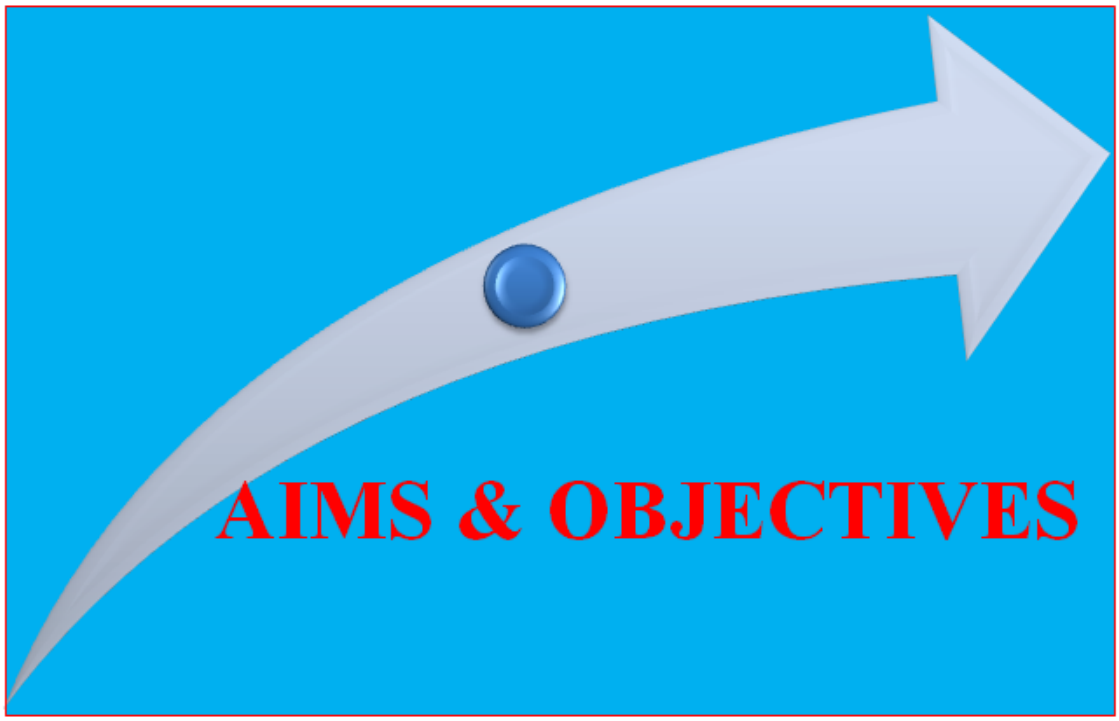
In 2009, van der Loos ML et al, stated that lamotrigine was found effective and safe as add-on treatment to lithium in the acute treatment of bipolar depression through a multicenter, double-blind, placebo-controlled trial to assess the efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression.[19]

In 2005, Biton V et al, stated that adjunctive lamotrigine is effective in the treatment of primary generalized tonic-clonic seizures and has a favorable tolerability profile through a double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures.[20]

In 1993, Matsuo F stated that lamotrigine was safe, effective, and well tolerated as add-on therapy for refractory partial seizures through a placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures.[21]

In 2007, Naritoku DK et al, stated that once-daily adjunctive lamotrigine extended-release compared with placebo effectively reduced partial seizure frequency and was well tolerated in a baseline phase, a 7-week double-blind escalation phase, and a 12-week double-blind trial.[22]

In 1999, Duchowny M et al, stated that lamotrigine was effective for the adjunctive treatment of partial seizures in children and demonstrated an acceptable safety profile through a placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children.[23]


AIMS & OBJECTIVES

3. AIM AND OBJECTIVES

Primary Objective:

To evaluate the relative bioavailability of Lamotrigine orally disintegrating tablets 50 mg, of Edict Pharmaceuticals, Chennai, India and LAMICTAL® ODT™ (Lamotrigine) Orally Disintegrating Tablets 50 mg of GlaxoSmithKline, Research Triangle Park, NC 27709 in healthy, adult, human subjects under fed conditions.

Secondary Objective:

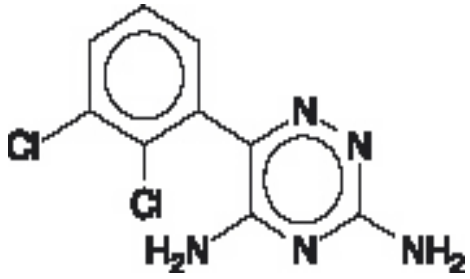
The other objectives of this study are to identify, assess, treat, and report any adverse events and ensure safety of the subjects during the course of the clinical study.


DRUG PROFILE

4.DRUG PROFILE

3.1 Description of the Investigational Product:

Lamotrigine chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pKa of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



3.2 Indications and Usage

Epilepsy

Adjunctive Therapy: Lamotrigine is indicated as adjunctive therapy for the following seizure types in patients 2 years of age: Partial seizures, Primary generalized tonic-clonic seizures, and Generalized seizures of Lennox-Gastaut syndrome.

Monotherapy: Lamotrigine is indicated for conversion to monotherapy in adults 16 years of age) with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug.

Bipolar Disorder

Lamotrigine is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes depression, mania, hypomania, mixed episodes in adults 18 years of age) treated for acute mood episodes with standard therapy.

3.3 Clinical Pharmacology

Mechanism of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in

preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

3.4 Pharmacokinetics:

Absorption

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent, whether they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets swallowed with water.

Distribution

Estimates of the mean apparent volume of distribution of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. volume of distribution is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Metabolism

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of 14C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine

(10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Elimination

The elimination half-life and apparent clearance of Lamotrigine following administration of Lamotrigine to adult healthy volunteers is summarized below.

Adult Study Population	Tmax: Time of Maximum Plasma Concentration (hr)	t½: Elimination Half-life (hr)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:			
Single-dose lamotrigine	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose lamotrigine	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)

3.5 Dosage Forms and Strengths

Tablets, Chewable Dispersible Tablets, and Chewable Dispersible Tablets: 25 mg, 100 mg, 150 mg, and 200 mg

3.6 Adverse Drug Reactions

Lamotrigine has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of adverse reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to lamotrigine who experienced an event of the type cited on at least one occasion while receiving lamotrigine. All reported adverse reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug.

Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole: Infrequent: Allergic reaction, chills, and malaise.

Cardiovascular System: Infrequent: Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation.

Dermatological: Infrequent: Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. Rare: Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson syndrome, and vesiculobullous rash.

Digestive System: Infrequent: Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. Rare: Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, and tongue edema.

Endocrine System: Rare: Goiter and hypothyroidism.

Hematologic and Lymphatic System: Infrequent: Ecchymosis and leukopenia. Rare: Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

Metabolic and Nutritional Disorders: Infrequent: Aspartate transaminase increased. Rare: Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

Musculoskeletal System: Infrequent: Arthritis, leg cramps, myasthenia, and twitching. Rare: Bursitis, muscle atrophy, pathological fracture, and tendinous contracture.

Nervous System: Frequent: Confusion and paresthesia. Infrequent: Akathisia, apathy, aphasia, central nervous system (CNS) depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation. Rare: delirium, delusions, dysphoria,

dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.

Respiratory System: Infrequent: Yawn. Rare: Hiccup and hyperventilation.

Special Senses: Frequent: Amblyopia. Infrequent: Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. Rare: Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect.

Urogenital System: Infrequent: Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, and urinary incontinence. Rare: Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, and urinary urgency.

3.7 Overdosage

Human Overdose Experience

Overdoses involving quantities up to 15 g have been reported for lamotrigine, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

Management of Overdose

There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A poison control center should be contacted for information on the management of overdosage of lamotrigine.

3.8 Use in Specific Populations

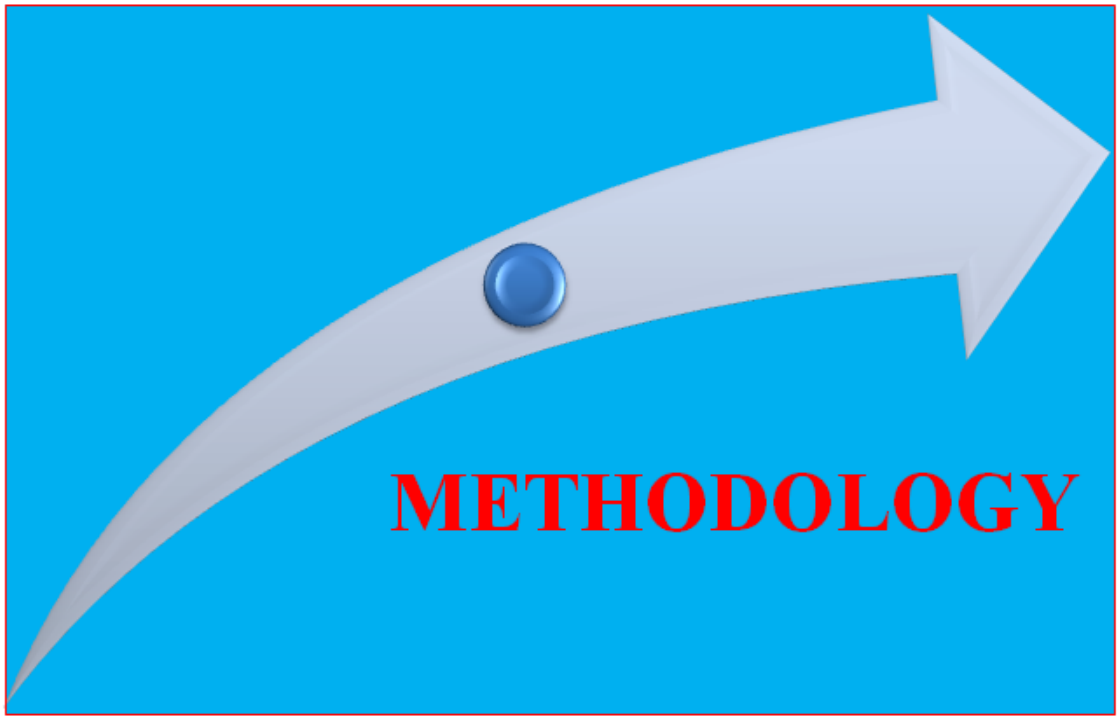
Pregnancy

Teratogenicity Effects: No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at

doses up to 1.2, 0.5, and 1.1 times, respectively, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased.

Labor and Delivery

The effect of LAMICTAL on labor and delivery in humans is unknown.


METHODOLOGY

5.METHODOLOGY

5.1 Investigational Plan

Overall Study Design and Plan

The study was an open-label, balanced, randomized, two-treatment, two-period, twosequence, single-dose, two-way crossover, bioequivalence study in healthy, adult, human subjects under fed conditions comparing equal doses of the test and reference products. Blood sampling was carried at pre-defined intervals up to 144.00 hours after dosing in each period. Subjects were confined at the clinical facility from at least 11.00 hours prior to dosing to at least 24.00 hours post dose. The interval between the two treatment period was 14 days.

Study Population: 32, healthy, adult, human subjects

Study type: Fed conditions

Discussion of Study Design and the Choice of Control Group

Edict Pharmaceuticals, Chennai, India seeks approval of a generic version of Lamotrigine tablets 50 mg for which demonstration of bioequivalence to the reference listed product.

LAMICTAL® ODT™ (Lamotrigine) Orally Disintegrating Tablets 50 mg of GlaxoSmithKline, Research Triangle Park, NC 27709 was required. After literature review and considering bioequivalence standards, intra-subject variability and possibility of drop outs, the protocol for study was written incorporating sufficient number of subjects to be enrolled in the study. The protocol was reviewed and approved by the IEC prior to commencement of the study. The study was designed based on the known pharmacokinetics profile of Lamotrigine tablets and general accepted standards for the conduct of bioequivalence studies.

Data from subjects who completed both the periods of the study was used in the pharmacokinetic and statistical evaluation according to the protocol. In order to minimize any possibility of a carryover effect as per protocol, 14 days washout period was maintained in this study. Bioequivalence was determined by statistical comparison of log-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the test and reference products for Lamotrigine.

5.2 Independent Ethics Committee (IEC)

The study protocol with informed consent documents (English and Vernacular languages) was reviewed and approved by Independent Ethics Committee (The Chennai Ethics Committee).

Ethical Conduct of the Study

The study was conducted as per the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2006), "Good Clinical Practices for clinical research India" guidelines - Schedule Y (Amended version 2005), ICH-GCP guidelines and accordance with the Declaration of Helsinki (Seoul, October 2008). No subject was enrolled into the study without obtaining written informed consent and subjects were under medical supervision throughout their stay in the clinical facility to ensure safety and well being of the subjects.

Subject Information and Consent

Written informed consent was obtained from each subject prior to screening and also prior to enrollment in to the study. Subjects were asked to read the informed consent documents which were followed by a presentation by the trained study personnel.

5.3 Selection of Study Population

All subjects underwent a screening procedure (performed within 29 days) prior to the start of the study. Medical history and detailed demographic data were recorded. Each subject underwent a complete general physical examination (including but may not be limited to an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems), vital sign assessments, 12-lead electrocardiogram (ECG), X-ray and clinical laboratory assessments. Further, the subjects were selected on the basis of following inclusion and exclusion criteria.

Inclusion Criteria

Volunteers meeting all of the following criteria were considered for enrollment in the study:

- Healthy human volunteers of age 18-45 years with a Body Mass Index (BMI) ranges between 18.50 kg/m^2 and 24.99 kg/m^2 (according to the formula of BMI = weight (kg) / $[height\ (m)]^2$).
- Subjects who have no evidence of underlying disease during screening and check-in and whose screening is performed within 29 days of check-in.

- Subjects whose screening laboratory values are within normal limits or considered by the Physician or Principal/Clinical Investigator to be of no clinical significance.
- Non- or ex-smokers. Ex-smokers are defined as someone who has completely stopped smoking for at least the past 03 months.
- Willing to take ovo-lacto vegetarian diet.
- Generally healthy as documented by the medical history, physical examination (including but may not be limited to an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems) and vital sign assessments.
- Generally healthy as documented by 12-lead electrocardiogram (ECG), X-Ray, and clinical laboratory assessments.
- Generally healthy as documented by gynecological examination and breast examination (for female subjects in period I only).
- Generally healthy as documented by Pregnancy test (for female subjects only).
- Any abnormalities/deviations from the acceptable range that might be considered clinically relevant by the study physician or investigator will be evaluated as individual cases.
- Female subjects within normal limits or clinically non-significant laboratory evaluation results for FSH & LH (for female subjects only).
- Female subjects of childbearing potential;
- Practicing an acceptable non-hormonal contraceptive method of birth control after consulting with principal investigator; and/or
- Surgically sterile (bilateral tubal ligation).

Exclusion Criteria

History or presence of significant:

- Evidence of allergy or known hypersensitivity to Lamotrigine or other related drugs.
- Patients with hepatic encephalopathy, cholestasis, myasthenia, pre-existing liver disease and recently overcome or active existing tinnitus.

- Any major illness in the last three months or any significant ongoing chronic medical illness.
- Renal or liver impairment.
- History of current gastro-intestinal diseases influencing drug absorption.
- History of drug abuse within 03 months (including benzodiazepines, opioids, cocaine, Barbiturates**,** THC and amphetamine etc.)
- History of alcohol addiction or abuse within the past one year.
- High caffeine (more than 05 cups of coffee or tea/day) or tobacco (more than 05 packets of gutka/day) consumption.
- Consumption of grapefruit and/ or its juice, and poppy containing foods within 72.00 hours prior to clinic admission and throughout the entire study.
- Subject who had participated in any other study within the 03 months of check-in.
- History of difficulty in swallowing.
- Any blood donation / excess blood loss within 03 months of check-in.
- History of difficulty in accessibility of veins.
- Ingestion of any hormonal agent at any time in 14 days prior to start of study.
- Pregnant females.
- Breast feeding females.
- Use of hormone replacement therapy within 06 months prior to dosing.
- Female subjects with child bearing potential using prohibited contraceptive method (oral, injectable or implantable hormonal agents).

Withdrawal Criteria

The investigator may withdraw a subject from the study for reasons which include but not limited to:

- Adverse event which warrants withdrawal of subject.
- Willful withholding of information by subjects.
- Failure of drug administration.
- Failure of cannulation.

- Undue difficulty in obtaining blood sample.
- Non-compliance with procedures.
- Premature termination of study.
- It is in the best interest of the study participant that he be withdrawn.
- Withdrawal of consent for participation in the study by the subject.
- Occurrence of emesis at or before two times of median $t_{max.}$
- The subject withdrawal during the study was handled as per in-house standard operating procedure with adequate documentation.

5.4 Treatments

The subjects were administered a single oral dose of test product Lamotrigine or the reference product LAMICTAL® ODT™ in sitting posture with about 20 mL of water to wet the mouth before drug administration . After swallowing of 20 mL of water oro-dispersible tablets of test or reference product was placed on the tongue of the subjects at the scheduled time of dosing and allowed to disintegrate on the tongue for 30 seconds. At the end of 30 seconds subject's tongue was checked for complete disintegration of the tablet. After disintegration of the tablet 220 mL of water was given at ambient temperature on period I and Period II under fed conditions. Compliance for dosing after drug administration was assessed by examination of the oral cavity by qualified study personnel. The order of receiving the test and reference product for each subject during the study was determined according to SAS® software (version 9.2) generated randomization schedule. The randomization was balanced and the code was kept under controlled access.

Treatments Administered

The subjects were given a single oral dose of either the test product [Lamotrigine tablets 50 mg] or reference product [LAMICTAL® ODT™ tablets, 50 mg] in each period as per the randomization schedule separated by a washout period of 14 days. Subjects S16 and Subject S30 did not report to the facility.

Method of Assigning Subjects to Treatment Groups

The eligible subjects, who fulfilled the inclusion and exclusion criteria for the study, were enrolled and randomly assigned to one of the possible sequences of test product (T) and reference product (R) (either TR or RT) in consecutive order using SAS® (SAS Institute Inc., USA) version 9.2.

The randomization was balanced and the code was kept under controlled access. The study personnel involved in the sample analysis were kept blinded from the randomization code during entire study.

Selection of Doses in the Study

As per the reference listed drug, regulatory recommendations, Lamotrigine tablets 50 mg was considered as relatively safe dose to administer in healthy, adult, human subjects and chosen to achieve sufficient plasma levels to characterize the pharmacokinetic profile.

Selection and Timing of Dose for Each Subject

The subjects were given a single oral dose of the test product Lamotrigine or reference product LAMICTAL® ODT™ 20 mL of water to wet the mouth before drug administration . After swallowing of 20 mL of water oro-dispersible tablets of test or reference product will be placed on the tongue of the subjects at the scheduled time of dosing and allowed to disintegrate on the tongue for 30 seconds. At the end of 30 seconds subject's tongue will be checked for complete disintegration of the tablet. After disintegration of the tablet 220 mL of water between (10.00 Hrs) to (10.22 Hrs) at staggered intervals as per the randomization schedule in each period with a washout period of 14 days. Individual demographic data of subjects can be found in table 1. The date and time of dosing of each subject for the two periods are given in the table 2.

Blinding

The study was an open label randomized study. Since bioequivalence studies involve a comparison of pharmacokinetic profiles, which are not subjective measurements, blinding was not deemed necessary for this study. However, bioanalytical analysts were blinded to the randomization during the course of the analysis and until the results were processed by the statistical department and reported.

Table 1 Individual Demographic Data of All Subjects (N=32) Participated in the Study

Subject No	Age (yrs)	Height (cm)	Weight (kg)	BMI (Kg/m^2)	Gender	Race	Smoking status
S01	25	170	57	19.72	Male	Asian	Non-smoker
S02	32	157	58	23.53	Male	Asian	Non-smoker
S03	40	167	68	24.38	Male	Asian	Non-smoker
S04	26	169	53	18.55	Male	Asian	Non-smoker
S05	33	165	68	24.97	Male	Asian	Non-smoker
S06	30	161	52	20.06	Male	Asian	Non-smoker
S07	37	173	74	24.72	Male	Asian	Non-smoker
S08	29	170	70	24.22	Male	Asian	Non-smoker
S09	23	179	72	22.47	Male	Asian	Non-smoker
S10	31	166	68	24.67	Male	Asian	Non-smoker
S11	21	174	61	20.14	Male	Asian	Non-smoker
S12	21	174	57	18.82	Male	Asian	Non-smoker
S13	20	160	51	19.92	Male	Asian	Non-smoker
S14	27	172	74	24.72	Male	Asian	Non-smoker
S15	32	169	70	24.5	Male	Asian	Non-smoker
S16	18	170	59	20.41	Male	Asian	Non-smoker
S17	19	172	56	18.92	Male	Asian	Non-smoker
S18	39	165	60	22.03	Male	Asian	Non-smoker
S19	26	173	85	28.4	Male	Asian	Non-smoker
S20	25	178	68	21.46	Male	Asian	Non-smoker
S21	41	176	76	24.53	Male	Asian	Non-smoker
S22	27	172	72	24.33	Male	Asian	Non-smoker
S23	24	168	63	22.32	Male	Asian	Non-smoker
S24	32	166	58	21.04	Male	Asian	Non-smoker
S25	25	178	63	19.88	Male	Asian	Non-smoker
S26	31	177	62	19.79	Male	Asian	Non-smoker
S27	38	178	76	23.98	Male	Asian	Non-smoker
S28	42	158	58	23.23	Male	Asian	Non-smoker
S29	19	174	57	18.82	Male	Asian	Non-smoker

Treatment Compliance

The trained clinical study personnel ensured that dosing was appropriately carried out by closely monitoring the subjects. Compliance for dosing after drug administration was assessed by examination of the oral cavity. The dosing was done by adequately trained personnel under the supervision of principal investigator/clinical investigator and quality assurance auditor. Dosing was done and the details were recorded in individual raw data forms.

Pharmacokinetic and Safety Variables

Pharmacokinetic and Safety Measurements

The study was designed to evaluate the relative bioavailability of test and reference products of Lamotrigine tablets 50 mg. Therefore efficacy was not measured, instead pharmacokinetic profile (in terms of rate and extent of absorption) of both test and reference products were evaluated based on measured concentration of drug in the human plasma sample collected in clinical phase.

Safety assessments were done based on clinical observations, laboratory data at the beginning and at the end of the study and evaluation of the AE's observed during the course of the study.

The date, time, randomization order and dosing status of subjects are described in table 2 . Schedule of assessment was described in table 3.

Table 2: **Date, Time of Dosing, Randomization order and Dosing Status of Subjects**

No.	Randomization Order		Scheduled Time of Dosing		Dosing Status	
	Period I	Period II	Period I (20 Dec 13)	Period II (03 Jan 2014)	Period I	Period II
S01	R	T	10:01	10:00	Dosed	Dosed
S02	T	R	10:03	10:02	Dosed	Dosed
S03	R	T	10:05	10:04	Dosed	Dosed
S04	T	R	10:06	10:06	Dosed	Dosed

No.	Randomization Order		Scheduled Time of Dosing		Dosing Status	
	Period I	Period II	Period I (20 Dec 13)	Period II (03 Jan 14)	Period I	Period II
S05	T	R	10:08	10:08	Dosed	Dosed
S06	R	T	10:10	10:10	Dosed	Dosed
S07	R	T	10:12	10:12	Dosed	Dosed
S08	T	R	10:14	10:14	Dosed	Dosed
S09	T	R	10:17	10:16	Dosed	Dosed
S10	R	T	10:18	10:19	Dosed	Dosed
S11	R	T	10:20	10:20	Dosed	Dosed
S12	T	R	10:22	10:22	Dosed	Dosed
S13	R	T	10:01	10:00	Dosed	Dosed
S14	T	R	10:03	10:02	Dosed	Dosed
S15	R	T	10:05	10:04	Dosed	Dosed
S16	T	Not reported	10:06	Not reported	Dosed	Not dosed
S17	T	R	10:08	10:08	Dosed	Dosed
S18	R	T	10:10	10:10	Dosed	Dosed
S19	R	T	10:12	10:12	Dosed	Dosed
S20	T	R	10:14	10:14	Dosed	Dosed
S21	R	T	10:16	10:16	Dosed	Dosed
S22	T	R	10:18	10:18	Dosed	Dosed
S23	R	T	10:00	10:00	Dosed	Dosed
S24	T	R	10:02	10:03	Dosed	Dosed
S25	R	T	10:04	10:05	Dosed	Dosed
S26	T	R	10:06	10:15	Dosed	Dosed
S27	T	R	10:08	10:09	Dosed	Dosed
S28	R	T	10:10	10:11	Dosed	Dosed
S29	T	R	10:12	10:13	Dosed	Dosed
S30	R	Not reported	10:14	Not reported	Dosed	Not dosed
S31	R	T	10:16	10:16	Dosed	Dosed
S32	T	R	10:18	10:18	Dosed	Dosed

Table 3: Schedule of assessment

Events → Assessment↓	Informed Consent followed by Screening	Period I				Wash out period	Period II				
		Informed Consent followed by Check-in	Dosing	Check-out	Ambulatory		Check-in	Dosing	Check-out	Ambulatory	Post-study assessment
Study days	-28 to 00 day	00	01	02	02,03,04, 05, 06, 07	00 to 14	14	15	16	16, 17, 18, 19, 20, 21	21
Medical history	✓	✓	N/AP	N/AP	N/AP	N/AP	✓	N/AP	N/AP	N/AP	N/AP
Physical examination	✓	✓	N/AP	✓	N/AP	N/AP	✓	N/AP	✓	N/AP	N/AP
Vitals	✓	✓	✓	✓	✓	N/AP	✓	✓	✓	✓	N/AP
Lab tests	✓	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	✓
X ray and ECG	✓	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
Urine screen for drugs of abuse	N/AP	✓	N/AP	N/AP	N/AP	N/AP	✓	N/AP	N/AP	N/AP	N/AP
Alcohol breath test	N/AP	✓	N/AP	N/AP	✓	N/AP	✓	N/AP	N/AP	✓	N/AP
Well being questionnaire	N/AP	N/AP	✓	✓	✓	N/AP	N/AP	✓	✓	✓	N/AP
Monitoring for AE	N/AP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Appropriateness of Measurements

The selection and timing of blood samples for pharmacokinetic analysis were judged appropriately for characterizing the pharmacokinetic profiles for given treatment and dose administered. The pharmacokinetic parameters used / derived in this study are widely used and accepted in the assessment of the pharmacokinetic equivalence of two treatments. The safety assessments conducted in this study were judged appropriately by the investigators and are documented in the raw data sheets / CRF's which served as source documents.

Primary Pharmacokinetic Variable(s)

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are the primary pharmacokinetic variables, as the 90 confidence intervals are applied for these parameters and t_{max}, $t_{1/2}$, $K_{el,}$ $K_{el\_Lower,}$ K_{el_Upper} and $AUC_{\_\%Extrap\_obs}$ was considered as secondary variables.

Drug Concentration Measurements

According to the guidelines, the determination of bioavailability is dependent on the reliable, precise and accurate measurement of the concentration levels of the active ingredient of the drug product in blood, plasma, serum or other biological matrices.

Totally 23 samples were collected per subject in each period. At pre-dose (00.00 hr), 00.25, 00.50, 00.75, 01.00, 01.50, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 and 144.00 hours after dosing. The volume of blood collected after dosing at each time point was 06 mL and post study assessments 08 mL of blood was collected. The total volume of blood collected from each subject throughout the study did not exceed 316 mL. Blood samples were drawn using sterile, disposable syringes from indwelling intravenous cannula placed in the cubital fossa and transferred into pre-labelled K_2EDTA Vacutainers. Vacutainers were placed upright in a rack kept in wet ice bath until centrifugation. Heparin-lock technique was used to prevent clotting of the blood in the indwelling catheter. Before each in-house blood draw, around 0.5 mL of blood was discarded to prevent the heparin in the catheter interfering during analysis. The details of sample collection were provided in table 4.

Table 4: Details of Sample Collection

Total No. of subjects as per protocol	32	
Total No. of subjects enrolled	32	
Total No. of periods	02	
Total No. of sampling points	23 / subject / period	
Total No. of samples to be collected (As Per Protocol)	1472	
Total No. of samples to be collected (As Per Subjects Enrolled)	1472	
Total No. of samples collected	(Period I) 715	1402
	(Period II) 687	
Total number of missing samples	70	

After collection of blood samples from all the subjects at each time point, the blood samples were centrifuged at 4000 RPM for 10 minutes at 4°C to separate the plasma and the plasma samples were transferred into pre-labeled polypropylene tubes into double aliquots. These samples were stored at temperature at (-)25°C at the clinical site. At the end of the study, samples were transferred to the bioanalytical facility and stored at a temperature below (-) 70^{o}C in ultra low temperature freezer until analysis. The pharmacokinetic parameters (Primary parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and Secondary parameters: t_{max}, $t_{1/2}$, K_{el}, K_{el_Lower}, K_{el_Upper} and $AUC_{\_\%Extrap\_obs}$) were estimated in order to characterize rate and extent of absorption of the investigational drug products.

Data Quality Assurance

The quality assurance unit played an integral role throughout the study. The conduct of the study and the data generated during the study, together with this report which reflect the raw data were inspected and audited by the quality assurance unit for conformance to study protocol, in house SOPs, GCP and GLP.

5.5 Statistical Methods Planned in the Protocol and Determination of Sample Size

Statistical and Analytical Plans

Statistical analysis was carried out using the SAS® statistical software, version: 9.2 of SAS Institute Inc, USA. The pharmacokinetic and statistical analyses were performed on subjects who completed both the periods of the study and who have been analyzed in the bioanalytical department. The descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean) for the pharmacokinetic parameters (primary parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and secondary parameters: t_{max}, $t_{1/2}$, K_{el}, $K_{el\_Lower,}$ K_{el_upper} and $AUC_{\_\%Extrap\_obs}$) were estimated for both test and reference products. The Ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using an ANOVA model. The analysis of variance model included sequence, subjects nested within sequence, period and treatment as factors. In order to test the two one-sided test for bioequivalence, 90% confidence intervals for the difference between the least square mean of treatment was calculated for Ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The confidence interval is expressed as percentage difference relative to the LSM of the reference treatments.

Determination of sample size

The sample size was based on:

- Expected range of test to reference ratio.
- Coefficient of variation (CV) of the drug.
- Sufficient statistical power to detect 20% difference with the power of 0.8 in C_{max} and AUC between test and reference products.
- Regulatory requirements.

Based on the above criteria, a sample size of 32 was chosen for this study.

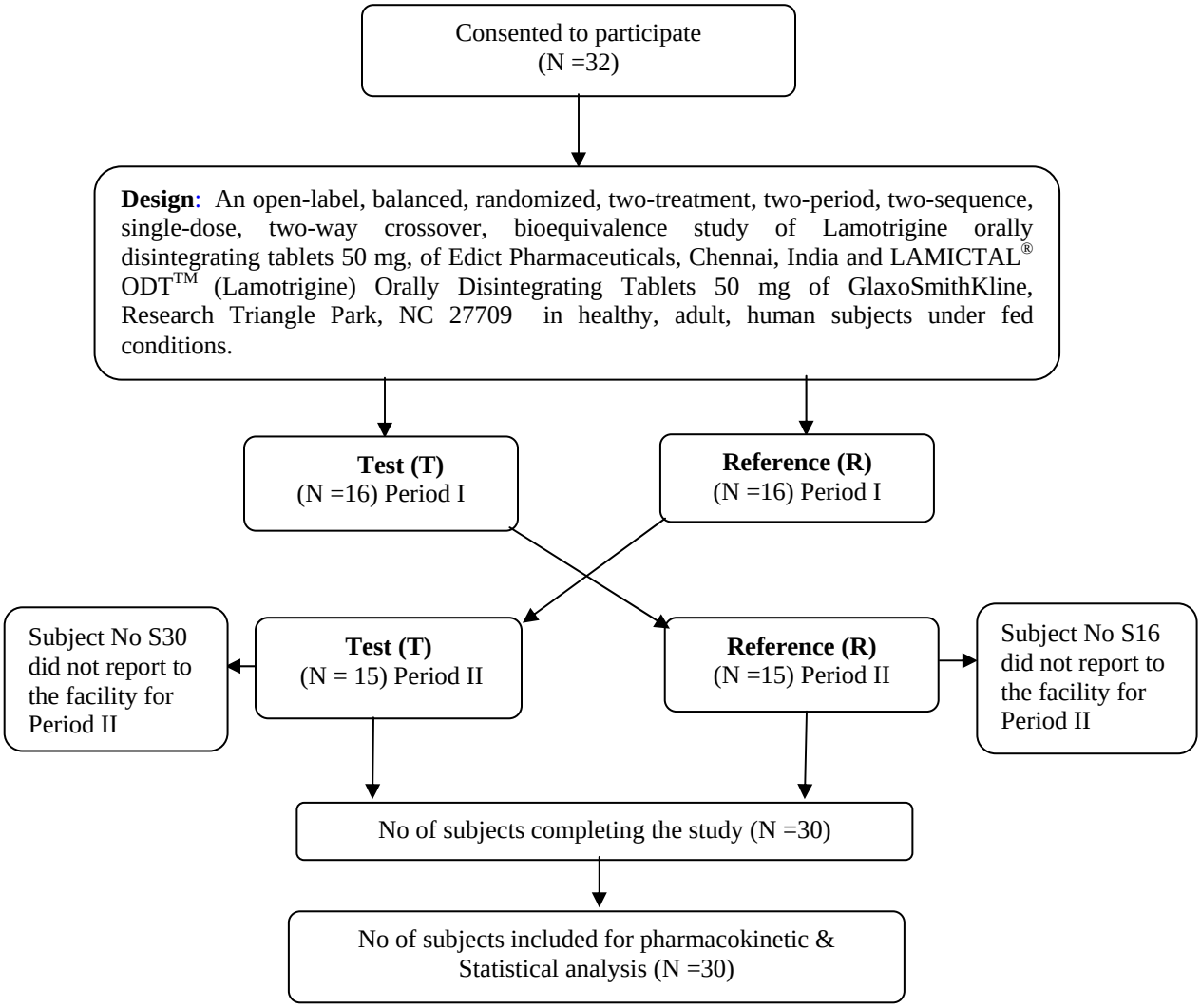
Changes in the Conduct of the Study

Nil

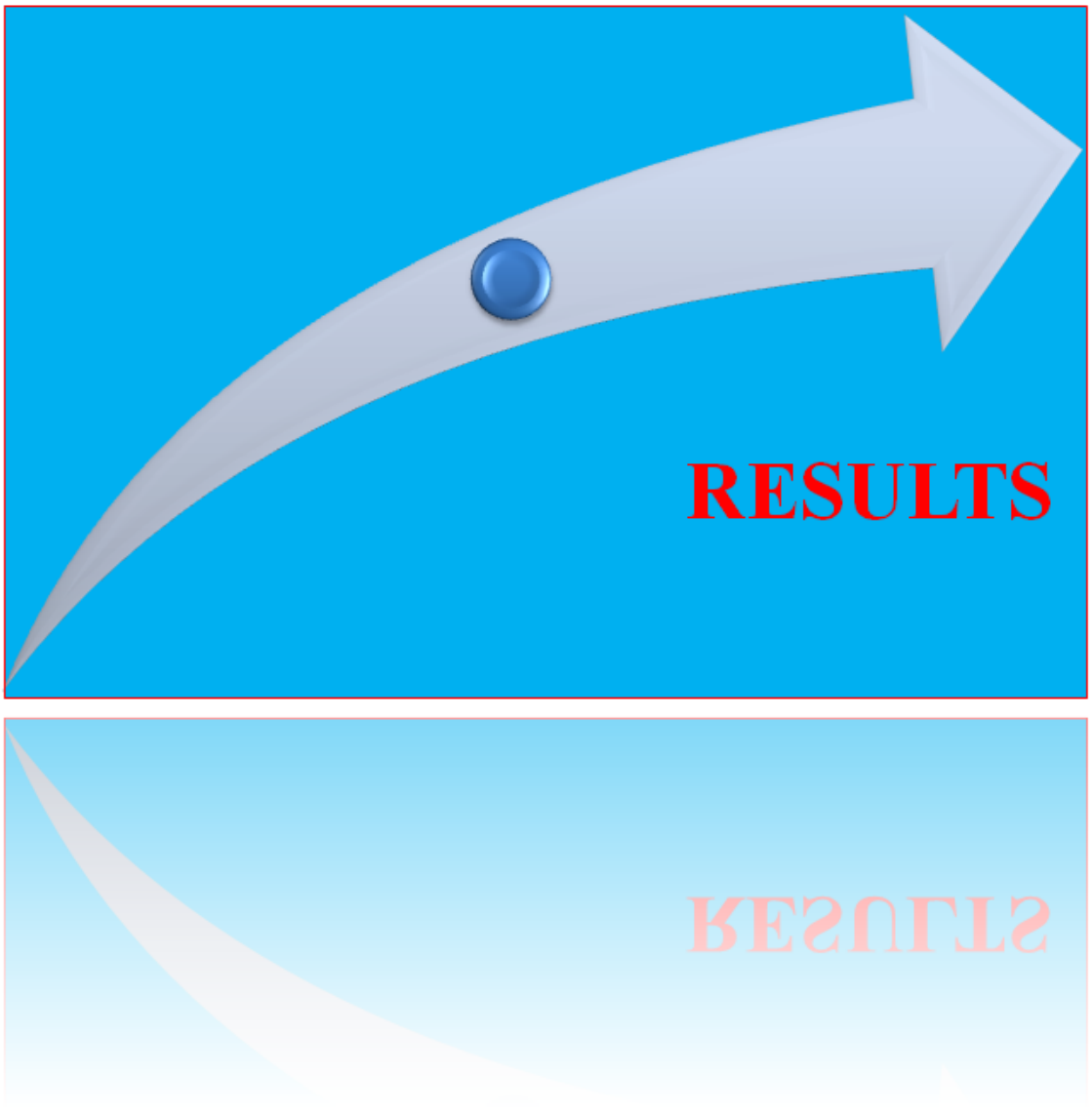
STUDY SUBJECTS

Disposition of Subjects

A total of 32 healthy, adult human subjects were enrolled into the study.



Test Product (T): Lamotrigine tablets 50 mg manufactured by Edict Pharmaceuticals, Pvt.Ltd **Reference Product (R):** LAMICTAL® ODT™ (Lamotrigine) Orally Disintegrating Tablets 50 mg of GlaxoSmithKline, Research Triangle Park, NC 27709.


RESULTS

6.RESULTS

6.1 PHARMACOKINETIC EVALUATION

Data Sets Analyzed

All the 32 enrolled into the study. Of the 32 enrolled subjects, 30 subjects have completed. Samples from 30 subjects who completed the study were analyzed to determine the concentrations of Lamotrigine. Pharmacokinetic and Statistical analysis were performed on data obtained from 30 subjects who completed the study. All concentration values below the lower limit of quantification (LLOQ) were set to "zero" for all pharmacokinetic and statistical calculations.

Demographic and Other Baseline Characteristics

A total of 32 subjects were enrolled into the study and their mean age, height, weight and BMI were 28.21years, 169.56 cm, 64.09 kg and 22.04 kg/m^2 respectively (Table 5). All subjects included in the study were Asian.

Table 5: Summarized Demographic Profile of Subjects

Demographic details of subjects who participated in the study (N=32)					
Parameter	**Mean**	**SD**	**Min**	**Max**	**CV%**
Age (years)	28.21	7.09	18	42	25.15
Height (cm)	169.56	6.01	157	179	8.65
Weight (Kg)	64.09	8.49	50	85	13.2
BMI (Kg/m^2)	22.04	2.26	18.55	24.97	10.27
Demographic details of subjects who were included in Pharmacokinetic and Statistical analysis (N=30)					
Parameter	**Mean**	**SD**	**Min**	**Max**	**CV%**
Age (years)	28.86	6.84	19	42	23.71
Height (cm)	169.80	6.05	157	179	3.56
Weight (Kg)	64.73	8.30	51	85	12.82
BMI (Kg/m^2)	22.43	2.51	19	28	11.19

Measurements of Treatment Compliance

The test and reference investigational drug products were administered as per the randomization schedule at scheduled time of dosing and there were no deviations in

drug dosing. The drug administration was done by the trained clinical study personnel under the supervision of principal investigator/clinical investigator qualified medical personnel and quality assurance auditor.

Pharmacokinetic Results and Tabulations of Individual Subject Data

The pharmacokinetic evaluation was carried out at Azidus Laboratories Private Limited, Chennai, India.

Time deviations during sampling were treated as follows:

The actual time of sample collected were used to calculate pharmacokinetic parameters, except for pre-dose samples, which were always reported as zero (00.00 hour), regardless of time deviations.

Pharmacokinetic and Statistical Analysis

The plasma concentrations (ng/mL) for test product (T) and reference product (R) are presented in table 6 and table 7. Pharmacokinetic parameters were calculated using WinNonlin® software (version 5.3).

The mean, standard deviation (SD), geometric mean, coefficient of variation (CV %), minimum, median, maximum for both test and reference products were calculated for C_{max}, AUC_{0-t} $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, K_{el}, $K_{el\_Lower,}$ K_{el_Upper} and $AUC_{\_\%Extrap\_obs}$. The calculation of these pharmacokinetic parameters is explained in table 8 and table 9. Summary of P_K Parameters of test and reference can be found in table 10.

Table 6: Individual Subject plasma Lamotrigine Concentrations for Reference Product (R)

Subject	Period	Sequence	Concentration (ng/mL)										
			Time (hr)										
			00.00	00.25	00.50	00.75	01.00	01.50	02.00	02.50	03.00	04.00	05.00
S01	P1	RT	0.0000	20.8249	111.6906	144.5240	185.2919	309.0141	375.7528	432.4957	515.0929	633.1102	610.7777
S02	P2	TR	0.0000	221.8911	255.9688	238.5916	275.5863	328.8530	395.3387	466.8757	558.3900	696.6379	728.2911
S03	P1	RT	0.0000	83.7472	107.1424	221.9649	421.9901	514.7738	594.7749	561.7125	548.7522	666.2595	600.6523
S04	P2	TR	0.0000	27.6265	115.6455	320.6157	465.6219	573.8004	804.9903	749.1385	865.7792	911.9164	686.0022
S05	P2	TR	0.0000	28.6770	65.1236	125.1161	235.2104	371.1068	367.0029	452.0485	468.9258	631.3911	564.0789
S06	P1	RT	0.0000	10.1709	66.8644	124.8643	158.8172	198.6625	277.4177	322.9101	386.7367	706.1143	799.5141
S07	P1	RT	0.0000	0.0000	69.1267	51.1692	83.9203	149.7109	246.0433	526.1606	502.5535	615.1124	617.1693
S08	P2	TR	0.0000	39.3839	119.1892	373.2450	419.3301	761.6984	895.4255	851.9083	990.4384	1068.7052	667.0030
S09	P2	TR	0.0000	21.1197	38.8141	166.9620	219.1438	433.5702	460.8607	573.6954	616.0181	741.9582	636.8978
S10	P1	RT	0.0000	26.7599	40.1706	92.0755	186.7741	228.0924	274.1369	291.7455	530.0032	683.1614	733.5562
S11	P1	RT	0.0000	60.8622	83.1457	169.8287	276.5016	493.9605	597.2409	625.2187	686.3983	721.0649	788.4956
S12	P2	TR	0.0000	111.0542	176.2670	231.9360	344.2079	410.0198	512.6462	638.4188	706.2136	643.6043	639.0473
S13	P1	RT	0.0000	13.7920	138.4423	125.2380	200.0351	556.3082	641.6744	723.5541	733.2981	839.2519	780.2720
S14	P2	TR	0.0000	82.0358	177.2475	263.9265	344.2463	309.8328	416.9759	498.5610	590.1040	725.2247	696.6080
S15	P1	RT	0.0000	12.6684	74.1833	214.5517	264.5958	349.5333	444.4666	538.3086	622.5123	788.2763	934.6100
S17	P2	TR	0.0000	26.1692	45.6544	81.8669	76.0894	88.0182	108.7450	118.1583	134.6661	276.6367	372.2172
S18	P1	RT	0.0000	0.0000	42.5295	66.3691	87.2241	189.0775	339.6244	482.3589	538.5866	831.5445	953.8982
S19	P1	RT	0.0000	99.8521	242.8791	274.4557	379.5948	431.6987	513.3112	639.6197	843.9835	980.9137	965.8487
S20	P2	TR	0.0000	130.2131	189.5634	398.6276	582.3830	535.3375	753.6918	864.6708	997.7684	1050.2917	960.1431
S21	P1	RT	0.0000	0.0000	91.0853	40.8165	91.6255	186.6496	322.2382	497.7203	469.6161	752.9886	883.1366

Table 6: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Reference Product (R) …… (Contd)

Subject	Period	Sequence	Concentration (ng/mL)										
			Time (hr)										
			00.00	**00.25**	**00.50**	**00.75**	**01.00**	**01.50**	**02.00**	**02.50**	**03.00**	**04.00**	**05.00**
S22	P2	TR	0.0000	204.2835	196.0470	309.5732	349.0475	416.2567	525.0390	600.4261	873.2222	1075.8287	1015.8822
S23	P1	RT	0.0000	163.1324	515.2994	632.2024	598.7349	692.7218	756.9067	864.9798	896.0114	1083.9593	1140.0921
S24	P2	TR	0.0000	215.6084	198.4274	251.9594	370.3540	366.0199	525.2591	623.2849	624.7862	925.1126	798.9364
S25	P1	RT	0.0000	9.6337	178.8684	547.4662	354.3962	630.3674	660.8515	755.0630	695.7893	818.1053	829.7091
S26	P2	TR	0.0000	0.0000	48.0348	82.0629	203.2466	334.9198	401.5256	622.6748	690.2441	723.4373	756.8766
S27	P2	TR	0.0000	82.0230	132.8945	315.6964	524.1084	750.8146	720.3603	678.6648	777.1369	860.0975	649.3920
S28	P1	RT	0.0000	107.9642	315.2834	372.4065	404.7512	530.2466	709.2109	926.3693	1006.2467	980.7263	930.1408
S29	P2	TR	0.0000	12.0117	55.6291	101.6460	160.5904	331.2862	451.8679	711.1694	754.4205	756.8450	861.9112
S31	P1	RT	0.0000	401.5277	465.1625	530.9713	439.9967	562.3867	701.4649	657.2774	679.8353	900.2588	766.6119
S32	P2	TR	0.0000	M	145.3581	200.8866	302.3790	505.1046	496.9061	604.6178	626.9570	1026.4372	702.9541
N			**30**	**29**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**
Mean			**0.0000**	**76.3115**	**150.0579**	**235.7205**	**300.1932**	**417.9948**	**509.7250**	**596.6602**	**664.3496**	**803.8324**	**769.0242**
SD			**0.0000**	**92.1200**	**116.6536**	**151.9885**	**145.0629**	**175.1657**	**187.4390**	**177.6951**	**193.6471**	**177.8827**	**160.1366**
Min			**0.0000**	**0.0000**	**38.8141**	**40.8165**	**76.0894**	**88.0182**	**108.7450**	**118.1583**	**134.6661**	**276.6367**	**372.2172**
Median			**0.0000**	**28.6770**	**117.4174**	**218.2583**	**289.4403**	**413.1383**	**504.7762**	**613.6463**	**653.3962**	**772.5607**	**761.7443**
Max			**0.0000**	**401.5277**	**515.2994**	**632.2024**	**598.7349**	**761.6984**	**895.4255**	**926.3693**	**1006.2467**	**1083.9593**	**1140.0921**
CV%			**NC**	**120.7158**	**77.7390**	**64.4783**	**48.3232**	**41.9062**	**36.7726**	**29.7816**	**29.1484**	**22.1293**	**20.8233**
Geometric Mean			**NC**	**NC**	**117.1980**	**189.5733**	**261.0645**	**376.1619**	**470.5376**	**561.7250**	**628.5215**	**780.7343**	**751.9330**

NC=Not Calculable, M=Missing

Table 6: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Reference Product (R) …… (Contd)

Subject	Period	Sequence	Concentration (ng/mL)											
			Time (hr)											
			06.00	08.00	10.00	12.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00
S01	P1	RT	586.7722	593.7416	558.2968	546.4092	468.1742	449.4412	405.9600	300.0454	229.6364	150.6860	78.0071	58.9960
S02	P2	TR	681.2346	645.2420	615.9841	604.8767	508.4187	516.0625	361.4457	260.6029	153.7312	76.3590	40.3426	22.8144
S03	P1	RT	608.1647	567.6743	527.7008	545.7265	460.0049	442.9969	355.6084	242.2070	146.6745	113.6640	45.5425	31.7123
S04	P2	TR	729.6131	687.1366	740.5875	769.9670	634.6268	618.2951	574.1783	464.0003	314.2460	224.1379	145.0400	93.8852
S05	P2	TR	615.5550	585.9940	569.5508	521.9667	403.8515	438.6316	355.7193	256.1220	167.3021	92.5079	57.7607	36.2249
S06	P1	RT	794.3800	743.2140	737.3856	683.1994	517.6004	589.1052	482.9579	398.1940	295.2162	159.9743	108.2227	68.1139
S07	P1	RT	603.1941	657.8857	550.5377	490.6173	365.5846	375.7668	278.5743	194.2217	91.5927	54.0293	19.6897	0.0000
S08	P2	TR	594.5199	460.0180	508.1895	353.8999	385.7755	317.8920	343.4151	158.3813	155.8259	101.6707	136.0766	36.3124
S09	P2	TR	625.3840	612.9443	563.7039	577.3473	445.6039	407.0922	314.5717	197.4950	111.2855	57.1921	31.7658	18.5754
S10	P1	RT	720.5821	688.4967	560.2339	610.3554	421.9672	418.4158	286.8229	206.8394	118.2621	59.5089	30.8631	13.2058
S11	P1	RT	755.5040	626.4586	611.0972	587.8449	455.4034	455.5472	362.0774	311.9311	M	120.7537	90.5040	51.7849
S12	P2	TR	535.1915	527.5999	532.9395	515.2967	378.5994	356.1156	M	M	152.2030	67.9675	51.7436	27.2370
S13	P1	RT	726.9908	648.4380	591.6569	511.5373	385.1993	386.2230	252.1357	160.3671	M	30.0166	M	M
S14	P2	TR	712.3834	646.1091	598.4914	603.2487	519.2462	449.8483	583.2171	250.3213	348.0840	216.1641	204.9454	152.4237
S15	P1	RT	854.6599	751.2552	698.2999	759.4457	674.1867	681.5705	559.4560	418.5206	276.9030	187.1565	133.4199	83.8675
S17	P2	TR	575.1907	749.1913	777.7613	789.4083	668.0560	708.9103	570.0556	479.6635	338.0569	228.8147	137.3909	100.1935
S18	P1	RT	868.3628	828.6324	796.7134	733.4488	755.7443	794.4585	523.1307	509.6868	361.2482	251.0154	150.8218	106.2130
S19	P1	RT	842.8140	757.3820	750.8929	757.6764	589.0068	587.9126	M	M	311.6778	155.0590	71.9166	M
S20	P2	TR	884.8672	897.8803	862.6888	798.0791	693.5190	674.7710	682.4603	457.3315	290.6565	181.2622	120.2592	86.6135
S21	P1	RT	785.0568	677.8103	670.2500	684.7978	528.2519	606.9666	409.9171	328.2462	198.5952	128.0974	M	M

Table 6: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Reference Product (R) …… (Contd)

Subject	Period	Sequence	Concentration (ng/mL)											
			Time (hr)											
			06.00	**08.00**	**10.00**	**12.00**	**16.00**	**24.00**	**36.00**	**48.00**	**72.00**	**96.00**	**120.00**	**144.00**
S22	P2	TR	1149.6729	917.2822	910.4406	868.9432	944.7254	757.1096	690.3876	605.1661	524.2901	452.1246	357.4192	202.0384
S23	P1	RT	1027.6945	940.4231	946.3374	949.5692	748.1632	828.3968	732.5982	478.2380	317.9284	246.2211	109.4709	27.3993
S24	P2	TR	803.6747	738.1582	732.2018	708.4489	585.1118	502.5547	444.6505	339.5311	177.3465	99.6263	52.9511	30.8017
S25	P1	RT	637.3873	774.6127	496.4239	504.7183	430.8786	451.9184	287.4239	198.4740	88.3303	M	M	13.7440
S26	P2	TR	781.7848	687.9326	694.0101	577.7045	544.3094	542.9419	400.7323	236.1438	176.1613	28.3562	23.3639	19.0905
S27	P2	TR	696.2695	688.8666	591.2237	581.3873	475.3304	448.0424	372.5831	228.5608	113.7459	67.9862	34.6206	21.3590
S28	P1	RT	856.5734	799.6563	747.4095	854.3534	660.4005	536.4307	411.4325	304.8670	154.4661	80.5784	M	21.6955
S29	P2	TR	715.8600	689.9496	771.2132	636.1203	559.7839	590.4697	387.5648	343.5523	184.5518	103.8609	62.3439	43.2195
S31	P1	RT	777.1396	715.6679	809.6332	635.6304	536.0459	539.0189	333.3971	258.1589	109.8649	59.8626	36.4872	14.9804
S32	P2	TR	885.4239	804.0708	817.5339	723.0739	670.7889	623.9527	529.5444	389.1481	348.9793	226.8655	168.1598	101.3519
N			**30**	**30**	**30**	**30**	**30**	**30**	**28**	**28**	**28**	**29**	**26**	**27**
Mean			**747.7300**	**703.6575**	**677.9796**	**649.5033**	**547.1453**	**536.5620**	**439.0006**	**320.5720**	**223.4594**	**138.6731**	**96.1203**	**54.9575**
SD			**138.1528**	**110.1955**	**125.2930**	**132.8153**	**136.2060**	**133.1226**	**132.8136**	**118.2363**	**107.2328**	**90.9258**	**73.8178**	**47.6113**
Min			**535.1915**	**460.0180**	**496.4239**	**353.8999**	**365.5846**	**317.8920**	**252.1357**	**158.3813**	**88.3303**	**28.3562**	**19.6897**	**0.0000**
Median			**728.3020**	**688.6817**	**682.1301**	**622.9929**	**523.7491**	**526.2466**	**403.3462**	**302.4562**	**180.9492**	**113.6640**	**74.9619**	**36.2249**
Max			**1149.6729**	**940.4231**	**946.3374**	**949.5692**	**944.7254**	**828.3968**	**732.5982**	**605.1661**	**524.2901**	**452.1246**	**357.4192**	**202.0384**
CV%			**18.4763**	**15.6604**	**18.4803**	**20.4488**	**24.8939**	**24.8103**	**30.2536**	**36.8829**	**47.9876**	**65.5684**	**76.7973**	**86.6330**
Geometric Mean			**736.1203**	**695.2346**	**667.0146**	**636.1131**	**531.9715**	**521.0659**	**420.9022**	**300.5100**	**200.2565**	**113.6250**	**74.6635**	**NC**

NC=Not Calculable, M=Missing

Table 7: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Test Product (T)

Subject	Period	Sequence	Concentration (ng/mL)										
			Time (hr)										
			00.00	00.25	00.50	00.75	01.00	01.50	02.00	02.50	03.00	04.00	05.00
S01	P2	RT	0.0000	43.3406	151.5375	183.9230	274.9655	306.6002	409.9274	477.2791	566.1203	661.5518	617.2407
S02	P1	TR	0.0000	45.3413	72.4236	162.0482	241.4220	352.6827	419.8404	456.1001	475.9830	648.2203	830.3812
S03	P2	RT	0.0000	327.6114	407.9092	467.2177	518.3833	523.6288	632.8476	648.8888	698.7194	787.1794	569.9577
S04	P1	TR	0.0000	39.2101	225.7612	324.6980	312.8713	465.9701	557.9967	738.8120	626.6330	814.5174	796.7807
S05	P1	TR	0.0000	36.9045	111.5931	201.9784	237.6004	413.7769	490.4158	515.8897	586.0399	658.8675	636.9965
S06	P2	RT	0.0000	72.8131	218.2346	336.4726	406.0354	448.0991	457.8720	542.6937	714.5665	661.3710	798.3499
S07	P2	RT	0.0000	247.4942	452.8022	361.8574	333.6644	423.3197	470.8961	474.7661	583.2848	694.5733	612.1553
S08	P1	TR	0.0000	178.0674	149.2245	193.8189	199.1886	280.4297	370.1235	661.8674	713.4776	691.1787	565.1883
S09	P1	TR	0.0000	188.9042	184.2310	214.9091	271.1026	365.4929	440.8151	448.1925	567.1390	594.6142	670.9853
S10	P2	RT	0.0000	73.2164	114.9691	155.9676	164.4904	350.0726	477.3590	543.4487	700.8296	712.0663	792.5082
S11	P2	RT	0.0000	179.3185	178.8946	325.7758	355.5154	408.0355	539.7943	603.0335	665.8930	712.1718	708.7040
S12	P1	TR	0.0000	151.1808	180.7985	269.2717	304.4113	449.6952	500.7856	560.3869	701.7693	654.1333	592.7438
S13	P2	RT	0.0000	22.3382	175.4634	439.1873	464.9158	530.1180	612.1261	799.3957	896.7195	1003.6217	870.3289
S14	P1	TR	0.0000	50.0422	159.5140	304.0323	300.7343	451.3508	521.2192	603.0374	703.5256	717.5147	783.6396
S15	P2	RT	0.0000	79.0448	291.4829	337.5399	400.2118	500.7247	571.0489	662.4817	732.9119	942.3253	946.9818
S17	P1	TR	0.0000	59.7386	326.2787	472.7285	570.0304	576.2559	680.1055	717.8819	751.8156	860.6010	881.5533
S18	P2	RT	0.0000	36.9408	178.5573	194.3890	355.8201	388.6448	526.6547	741.8306	962.7772	1112.4377	881.9563
S19	P2	RT	0.0000	108.3154	303.9433	398.6143	489.5564	508.3539	558.5124	711.3650	851.5196	1037.6480	906.7425
S20	P1	TR	0.0000	0.0000	0.0000	112.6420	210.4587	320.2085	454.0248	551.9176	800.0866	835.7362	1021.9500
S21	P2	RT	0.0000	191.5354	215.1128	383.9041	421.9661	507.4575	583.9137	737.5436	701.0023	790.4101	585.7276

Table 7: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Test Product (T) …… (Contd)

Subject	Period	Sequence	Concentration (ng/mL)										
			Time (hr)										
			00.00	**00.25**	**00.50**	**00.75**	**01.00**	**01.50**	**02.00**	**02.50**	**03.00**	**04.00**	**05.00**
S22	P1	TR	0.0000	24.4285	41.0672	194.6128	258.9891	416.4356	608.3675	755.8535	867.3997	993.9692	1043.3088
S23	P2	RT	0.0000	127.4050	244.5804	278.1466	369.4580	402.6229	643.9728	759.4297	775.9478	1003.7225	1087.3276
S24	P1	TR	0.0000	385.4698	345.2920	571.0513	578.8704	728.7722	827.3088	879.6360	843.2931	939.4123	921.0403
S25	P2	RT	0.0000	0.0000	82.2098	127.5654	208.1953	374.4958	378.5859	467.4766	627.9835	761.1336	900.0824
S26	P1	TR	0.0000	498.0869	398.2702	452.9894	497.4248	566.6656	699.1959	702.7883	707.4488	786.8731	688.9322
S27	P1	TR	0.0000	194.9346	557.5513	554.5453	691.1304	710.0347	659.5843	779.3247	856.3887	855.0734	738.8795
S28	P2	RT	0.0000	140.2160	261.8981	230.0554	290.8783	487.2773	552.6067	633.8479	760.8936	1011.5064	964.5760
S29	P1	TR	0.0000	20.8229	119.3977	200.8651	315.4483	367.7002	500.1247	583.6504	621.9431	850.1370	860.4825
S31	P2	RT	0.0000	74.5858	246.7300	464.6663	395.2416	696.2141	663.1204	846.3129	657.8550	908.0623	928.5160
S32	P1	TR	0.0000	144.2717	283.3177	520.4269	431.6728	614.5262	684.2418	836.6752	818.6967	847.6750	940.2929
N			**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**
Mean			**0.0000**	**124.7193**	**222.6349**	**314.5300**	**362.3551**	**464.5221**	**549.7796**	**648.0602**	**717.9555**	**818.2768**	**804.8103**
SD			**0.0000**	**117.7980**	**125.5279**	**133.5768**	**126.9664**	**116.7332**	**107.1577**	**126.4132**	**112.0096**	**139.6663**	**151.7412**
Min			**0.0000**	**0.0000**	**0.0000**	**112.6420**	**164.4904**	**280.4297**	**370.1235**	**448.1925**	**475.9830**	**594.6142**	**565.1883**
Median			**0.0000**	**76.8153**	**199.6719**	**314.3652**	**344.5899**	**448.8972**	**546.2005**	**655.3781**	**705.4872**	**802.4638**	**814.3656**
Max			**0.0000**	**498.0869**	**557.5513**	**571.0513**	**691.1304**	**728.7722**	**827.3088**	**879.6360**	**962.7772**	**1112.4377**	**1087.3276**
CV%			**NC**	**94.4505**	**56.3829**	**42.4687**	**35.0392**	**25.1297**	**19.4910**	**19.5064**	**15.6012**	**17.0683**	**18.8543**
Geometric Mean			**NC**	**NC**	**NC**	**286.1901**	**341.6834**	**451.1601**	**539.8177**	**635.8432**	**709.3761**	**806.9553**	**790.4971**

NC=Not Calculable

Table 7: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Test Product (T) …… (Contd)

Subject	Period	Sequence	Concentration (ng/mL)											
			Time (hr)											
			06.00	08.00	10.00	12.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00
S01	P2	RT	691.5759	812.0812	545.7473	524.6047	449.7609	487.7706	371.1852	298.0857	193.9889	144.1451	92.1234	53.7406
S02	P1	TR	788.5166	718.0456	619.5282	647.6275	542.8373	501.6051	362.7632	267.4710	149.8872	98.5555	51.9421	32.6189
S03	P2	RT	653.1599	656.1173	603.1861	586.3209	497.5262	476.7147	432.2614	298.2050	179.4146	134.6435	93.0129	66.9511
S04	P1	TR	811.8905	736.7240	777.2833	685.5268	675.4288	754.1695	597.8947	498.5594	357.8196	277.0965	167.5461	99.6783
S05	P1	TR	637.5306	574.0917	576.8831	583.9424	450.4366	441.8319	389.2902	276.3152	222.2946	125.9456	60.0624	35.9083
S06	P2	RT	658.9468	647.5412	576.8712	554.5407	483.4382	522.6969	460.8402	448.2600	230.1736	149.5912	100.9213	72.2526
S07	P2	RT	782.6899	850.3078	698.1424	660.8120	595.5466	556.2561	435.1233	261.7564	143.9685	69.7651	37.7705	12.9031
S08	P1	TR	523.2538	734.5392	886.8234	639.0565	481.9045	556.9068	448.6881	356.8158	116.3618	63.0924	37.9943	19.6743
S09	P1	TR	629.7778	623.3042	686.2809	559.7362	505.4521	387.6051	288.8008	206.9993	118.4716	69.4297	32.4594	26.6944
S10	P2	RT	602.9519	596.7802	581.8085	567.6669	486.3650	456.5752	298.1240	188.6557	143.5428	67.2840	39.3819	19.1502
S11	P2	RT	672.4355	630.4944	605.7067	559.5370	496.1653	504.4954	388.8740	279.3953	184.8565	113.3477	87.3769	51.7249
S12	P1	TR	590.3046	477.7074	495.3927	471.8818	361.3221	378.1678	268.2028	274.5817	177.4558	96.5139	57.3880	37.6330
S13	P2	RT	741.3575	509.4374	660.7733	587.8066	488.9371	431.4927	234.5785	165.3809	64.9972	28.9922	0.0000	0.0000
S14	P1	TR	782.6232	632.2912	719.4948	693.0756	593.0592	576.0973	510.2070	439.0013	301.6217	232.3118	227.9634	219.5064
S15	P2	RT	888.7488	853.5711	840.5985	759.3445	623.9342	661.8118	520.0959	422.6767	254.9946	152.5027	96.0039	68.2610
S17	P1	TR	877.3714	806.4176	789.9520	769.9867	738.6568	703.9098	614.0404	454.9825	330.7047	253.4793	148.4803	97.3865
S18	P2	RT	940.9542	881.1734	862.3606	668.1197	616.7434	640.1671	522.4238	446.5945	297.5966	181.8335	130.3545	70.8983
S19	P2	RT	869.9400	796.1953	742.7764	720.1409	614.6505	624.9409	538.7249	332.7906	243.5959	159.9472	92.5653	53.9243
S20	P1	TR	947.3449	799.0589	847.0843	715.7568	603.8162	733.7847	M	M	320.5126	224.9888	137.3563	M
S21	P2	RT	702.0179	677.9977	659.2648	647.1447	539.6727	494.4593	404.8050	286.2527	202.4219	108.9233	73.5491	42.8669

Table 7: Individual Subject plasma Lamotrigine Concentrations (ng/mL) for Test Product (T) …… (Contd)

Subject	Period	Sequence	Concentration (ng/mL)											
			Time (hr)											
			06.00	08.00	10.00	12.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00
S22	P1	TR	983.6242	923.3912	939.5418	925.2133	895.7744	876.5013	771.2606	695.4014	580.0574	435.1824	M	M
S23	P2	RT	1170.1828	1050.7534	1016.5133	1117.2163	932.3338	883.9973	616.3306	624.4692	475.1715	298.4778	195.1044	139.2704
S24	P1	TR	840.3496	794.7307	712.0720	698.0321	518.7630	588.4065	497.2132	307.1329	176.0820	120.8769	58.0277	36.8374
S25	P2	RT	770.0082	686.0833	689.6579	624.2284	451.1862	485.9651	315.4169	283.1021	99.3493	49.8547	29.6638	20.1901
S26	P1	TR	530.8723	665.4680	648.8878	635.3195	507.2272	418.8603	369.4845	229.7312	139.3577	70.7758	30.0232	12.2660
S27	P1	TR	725.0394	656.3708	610.8099	624.0856	493.0512	451.3715	366.7162	266.6128	130.3501	74.7562	39.9768	24.8356
S28	P2	RT	924.8163	794.7485	823.1604	784.0736	569.6347	466.2106	410.5586	269.0333	129.4820	60.6541	34.9372	16.1103
S29	P1	TR	812.3710	819.1004	804.5021	645.8845	538.9373	511.9603	432.6235	319.9352	125.5459	79.0559	43.1647	M
S31	P2	RT	931.5878	861.7819	793.7934	766.1300	694.5569	578.3981	435.0264	290.1244	137.3027	76.7948	37.8597	15.5327
S32	P1	TR	807.1777	846.4278	825.8647	785.5752	694.3017	760.0040	679.9390	453.0536	379.3749	263.0406	157.1931	140.0893
N			**30**	**30**	**30**	**30**	**30**	**30**	**29**	**29**	**30**	**30**	**29**	**27**
Mean			**776.3140**	**737.0911**	**721.3587**	**673.6129**	**571.3807**	**563.7711**	**447.6377**	**342.8061**	**220.2251**	**142.7286**	**82.4208**	**55.0706**
SD			**146.9332**	**127.6059**	**126.2781**	**126.2559**	**126.2884**	**135.4899**	**125.6859**	**123.7596**	**117.2020**	**92.3802**	**56.1272**	**49.1750**
Min			**523.2538**	**477.7074**	**495.3927**	**471.8818**	**361.3221**	**378.1678**	**234.5785**	**165.3809**	**64.9972**	**28.9922**	**0.0000**	**0.0000**
Median			**782.6566**	**735.6316**	**705.1072**	**647.3861**	**539.3050**	**517.3286**	**432.6235**	**298.0857**	**182.1356**	**117.1123**	**60.0624**	**37.6330**
Max			**1170.1828**	**1050.7534**	**1016.5133**	**1117.2163**	**932.3338**	**883.9973**	**771.2606**	**695.4014**	**580.0574**	**435.1824**	**227.9634**	**219.5064**
CV%			**18.9270**	**17.3121**	**17.5056**	**18.7431**	**22.1023**	**24.0328**	**28.0776**	**36.1019**	**53.2192**	**64.7244**	**68.0984**	**89.2946**
Geometric Mean			**763.0077**	**726.1753**	**710.7889**	**663.5286**	**559.3858**	**549.3644**	**431.1089**	**323.9835**	**195.1578**	**118.6067**	**NC**	**NC**

NC=Not Calculable, M=Missing

Table 8: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Test Product -T)

Subject	Sequence	Test Product (T)					
		C_{max} (ng/mL)	AUC_{0-t} (ng*hr /mL)	AUC_{0-inf} (ng*hr /mL)	t_{max} (hr)	K_{el} $(hr)^{-1}$	$t_{½}$ (hr)
S01	RT	812.0812	36115.3776	38743.3935	8.00	0.0204	33.8962
S02	TR	830.3812	33249.8528	34687.0173	5.00	0.0227	30.5396
S03	RT	787.1794	37504.8163	42197.9467	4.00	0.0143	48.5882
S04	TR	814.5174	57506.0080	62198.4389	4.00	0.0212	32.6304
S05	TR	658.8675	34453.1271	35846.6673	4.00	0.0258	26.8999
S06	RT	798.3499	42361.2905	46775.4017	5.00	0.0164	42.3463
S07	RT	850.3078	34510.6106	34935.3693	8.00	0.0304	22.8178
S08	TR	886.8234	34121.3035	34931.9277	10.00	0.0243	28.5592
S09	TR	686.2809	27393.7133	28507.6897	10.00	0.0240	28.9255
S10	RT	792.5082	28573.2984	29276.0111	5.00	0.0273	25.4349
S11	RT	712.1718	35790.5623	38590.2426	4.00	0.0185	37.5175
S12	TR	701.7693	29363.7598	31128.1786	3.00	0.0213	32.4981
S13	RT	1003.6217	24072.7977	24896.2493	4.00	0.0352	19.6871
S14	TR	783.6396	53221.9294	75181.5522	5.02	0.0100	69.3431
S15	RT	946.9818	47908.3624	51429.4955	5.00	0.0194	35.7549
S17	TR	881.5533	56298.3055	62680.0901	5.00	0.0153	45.4223
S18	RT	1112.4377	50895.0567	54877.9671	4.00	0.0178	38.9395
S19	RT	1037.6480	45664.9808	47947.4694	4.00	0.0236	29.3393
S20	TR	1021.9500	53154.5782	61222.7810	5.00	0.0170	40.7149
S21	RT	790.4101	36695.0736	38827.8709	4.00	0.0201	34.4868

Table 8: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Test Product - T) (contd……)

Subject	Sequence	Test Product (T)					
		C_{max} (ng/mL)	AUC_{0-t} (ng*hr /mL)	AUC_{0-inf} (ng*hr /mL)	t_{max} (hr)	K_{el} (hr)-1	$t_{½}$ (hr)
S22	TR	1043.3088	66973.6420	117166.2751	5.00	0.0087	79.9455
S23	RT	1170.1828	71363.7186	79536.8531	6.00	0.0170	40.6776
S24	TR	939.4123	40806.6000	42397.9544	4.00	0.0231	29.9436
S25	RT	900.0824	29758.1484	30496.2816	5.00	0.0274	25.3409
S26	TR	786.8731	31113.1712	31448.4140	4.00	0.0366	18.9444
S27	TR	856.3887	32334.8946	33348.5118	3.00	0.0245	28.2895
S28	RT	1011.5064	34109.0017	34667.2840	4.00	0.0289	24.0201
S29	TR	860.4825	34126.4347	36104.8419	5.00	0.0218	31.7697
S31	RT	931.5878	37332.5234	37874.4828	6.00	0.0287	24.1850
S32	TR	940.2929	59487.7134	69639.7591	5.00	0.0138	50.2313
N		**30**	**30**	**30**	**30**	**30**	**30**
Arithmetic Mean		**878.3199**	**41208.6884**	**46252.0806**	**5.10**	**0.0219**	**35.2563**
Standard Deviation		**126.7126**	**12251.5909**	**19741.5045**	**1.75**	**0.0066**	**13.4131**
Minimum		**658.8675**	**24072.7977**	**24896.2493**	**3.00**	**0.0087**	**18.9444**
Median		**858.4356**	**36405.2256**	**38666.8181**	**5.00**	**0.0216**	**32.1339**
Maximum		**1170.1828**	**71363.7186**	**117166.2751**	**10.00**	**0.0366**	**79.9455**
CV (%)		**14.4267**	**29.7306**	**42.6824**	**34.29**	**30.1544**	**38.0446**
Geometric Mean		**869.6279**	**39619.8622**	**43173.8702**	**4.87**	**0.0208**	**33.3122**

Table 8: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Test Product - T) (contd……)

Subject	Sequence	Test Product (T)		
		$AUC_{\_Extrap\ (\%)}$	K_{el_Lower} (hr)	K_{el_Upper} (hr)
S01	RT	6.78	96.22	144.50
S02	TR	4.14	8.00	143.13
S03	RT	11.12	74.05	144.27
S04	TR	7.54	95.75	143.87
S05	TR	3.89	71.53	143.80
S06	RT	9.44	72.50	143.70
S07	RT	1.22	24.00	144.32
S08	TR	2.32	71.60	143.92
S09	TR	3.91	12.00	143.92
S10	RT	2.40	71.77	144.37
S11	RT	7.25	4.00	144.87
S12	TR	5.67	48.48	144.12
S13	RT	3.31	36.43	96.80
S14	TR	29.21	5.02	143.67
S15	RT	6.85	24.00	144.37
S17	TR	10.18	5.00	144.23
S18	RT	7.26	24.00	144.68
S19	RT	4.76	97.55	143.57
S20	TR	13.18	24.00	120.68
S21	RT	5.49	6.00	143.83

Table 8: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Test Product - T) (contd……)

Subject	Sequence	Test Product (T)		
		AUC_Extrap (%)	K_{el_Lower} (hr)	K_{el_Upper} (hr)
S22	TR	42.84	10.00	96.67
S23	RT	10.28	72.33	144.60
S24	TR	3.75	24.00	145.58
S25	RT	2.42	6.00	144.30
S26	TR	1.07	97.67	145.57
S27	TR	3.04	5.00	144.73
S28	RT	1.61	4.00	144.83
S29	TR	5.48	71.38	120.35
S31	RT	1.43	6.00	145.37
S32	TR	14.58	5.00	143.32
N		**30**	**30**	**30**
Arithmetic Mean		**7.75**	**39.11**	**139.53**
Standard Deviation		**8.65**	**34.82**	**13.11**
Minimum		**1.07**	**4.00**	**96.67**
Median		**5.49**	**24.00**	**144.18**
Maximum		**42.84**	**97.67**	**145.58**
CV (%)		**111.72**	**89.03**	**9.40**
Geometric Mean		**5.24**	**22.25**	**138.81**

Table 9: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Reference Product -R)

Subject	Sequence	Reference Product (R)					
		C_{max} (ng/mL)	AUC_{0-t} (ng*hr /mL)	AUC_{0-inf} (ng*hr /mL)	t_{max} (hr)	K_{el} $(hr)^{-1}$	$t_{½}$ (hr)
S01	RT	633.1102	36195.0890	39701.8545	4.00	0.0168	41.2012
S02	TR	728.2911	31970.0258	32852.7001	5.00	0.0258	26.8174
S03	RT	666.2595	30927.0913	32408.5412	4.00	0.0214	32.3806
S04	TR	911.9164	52571.5502	57757.5128	4.00	0.0181	38.2876
S05	TR	631.3911	30880.2038	32714.8000	4.00	0.0197	35.1042
S06	RT	799.5141	44690.3121	48514.5453	5.00	0.0178	38.9165
S07	RT	657.8857	23314.8001	23976.1187	8.00	0.0298	23.2808
S08	TR	1068.7052	30240.7050	32421.9814	4.00	0.0166	41.6372
S09	TR	741.9582	26894.0808	27697.8561	4.00	0.0231	29.9931
S10	RT	733.5562	26630.6338	27105.1957	5.00	0.0278	24.9088
S11	RT	788.4956	36470.5339	39373.4096	5.00	0.0178	38.8553
S12	TR	706.2136	28156.7668	29428.9718	3.00	0.0214	32.3760
S13	RT	839.2519	23059.8256	23915.2845	4.00	0.0351	19.7544
S14	TR	725.2247	47738.3215	61977.7877	4.00	0.0107	64.7540
S15	RT	934.6100	49850.4950	54903.6285	5.02	0.0166	41.7631
S17	TR	789.4083	51971.2210	58080.5863	12.00	0.0164	42.2651
S18	RT	953.8982	57020.8079	63370.8003	5.00	0.0167	41.4401
S19	RT	980.9137	46324.9030	48696.5284	4.00	0.0303	22.8582
S20	TR	1050.2917	54436.6970	59532.9962	4.00	0.0170	40.7845
S21	RT	883.1366	34799.8973	41538.5059	5.00	0.0190	36.4633

Table 9: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Reference Product -R) (Contd……)

Subject	Sequence	Reference Product (R)					
		C_{max} (ng/mL)	AUC_{0-t} (ng*hr /mL)	AUC_{0-inf} (ng*hr /mL)	t_{max} (hr)	K_{el} (hr)-1	$t_{½}$ (hr)
S22	TR	1149.6729	78614.9358	99251.5238	6.00	0.0098	70.7994
S23	RT	1140.0921	60538.1342	61137.6709	5.00	0.0457	15.1671
S24	TR	925.1126	37869.0130	39113.7060	4.00	0.0247	28.0100
S25	RT	829.7091	27423.7735	27918.4051	5.00	0.0278	24.9456
S26	TR	781.7848	31897.7636	34223.2373	5.98	0.0082	84.4344
S27	TR	860.0975	30285.9196	31201.6374	4.00	0.0233	29.7171
S28	RT	1006.2467	37901.5774	38703.1228	3.00	0.0271	25.6085
S29	TR	861.9112	37880.2634	39914.8532	5.00	0.0212	32.6304
S31	RT	900.2588	32041.0474	32569.8834	4.00	0.0283	24.4694
S32	TR	1026.4372	52621.0635	59592.0038	4.00	0.0145	47.6744
N		**30**	**30**	**30**	**30**	**30**	**30**
Arithmetic Mean		**856.8452**	**39707.2484**	**43319.8550**	**4.80**	**0.0216**	**36.5766**
Standard Deviation		**146.3876**	**13022.9511**	**16520.9636**	**1.67**	**0.0078**	**14.9673**
Minimum		**631.3911**	**23059.8256**	**23915.2845**	**3.00**	**0.0082**	**15.1671**
Median		**849.6747**	**36332.8115**	**39243.5578**	**4.00**	**0.0205**	**33.8673**
Maximum		**1149.6729**	**78614.9358**	**99251.5238**	**12.00**	**0.0457**	**84.4344**
CV (%)		**17.0845**	**32.7974**	**38.1372**	**34.77**	**36.1960**	**40.9204**
Geometric Mean		**844.8876**	**37863.1982**	**40744.7497**	**4.61**	**0.0203**	**34.1400**

Table 9: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Reference Product -R) (Contd……)

Subject	Sequence	Reference Product (R)		
		$AUC_{\_Extrap\ (\%)}$	K_{el_Lower} (hr)	K_{el_Upper} (hr)
S01	RT	8.83	4.00	143.12
S02	TR	2.69	24.00	144.22
S03	RT	4.57	4.00	143.17
S04	TR	8.98	96.50	144.55
S05	TR	5.61	96.75	144.23
S06	RT	7.88	95.80	143.73
S07	RT	2.76	24.00	120.13
S08	TR	6.73	5.00	144.10
S09	TR	2.90	95.60	144.27
S10	RT	1.75	24.00	143.95
S11	RT	7.37	24.00	144.33
S12	TR	4.32	6.00	144.67
S13	RT	3.58	35.47	96.03
S14	TR	22.98	4.00	145.20
S15	RT	9.20	48.32	143.60
S17	TR	10.52	24.00	143.83
S18	RT	10.02	48.58	144.15
S19	RT	4.87	72.35	120.67
S20	TR	8.56	71.90	143.55
S21	RT	16.22	35.00	96.73

Table 9: Comparative Evaluation of Pharmacokinetic Parameters for lamotrigine (Reference Product -R) (Contd……)

Subject	Sequence	Reference Product (R)		
		AUC_Extrap (%)	K_{el_Lower} (hr)	K_{el_Upper} (hr)
S22	TR	20.79	8.00	143.90
S23	RT	0.98	97.58	145.58
S24	TR	3.18	35.82	144.63
S25	RT	1.77	35.40	144.52
S26	TR	6.80	96.28	144.47
S27	TR	2.93	72.07	144.98
S28	RT	2.07	35.43	144.62
S29	TR	5.10	6.00	144.20
S31	RT	1.62	4.00	143.75
S32	TR	11.70	6.00	144.17
N		**30**	**30**	**30**
Arithmetic Mean		**6.91**	**41.20**	**139.44**
Standard Deviation		**5.42**	**34.53**	**13.17**
Minimum		**0.98**	**4.00**	**96.03**
Median		**5.35**	**35.20**	**144.16**
Maximum		**22.98**	**97.58**	**145.58**
CV (%)		**78.50**	**83.82**	**9.45**
Geometric Mean		**5.21**	**24.82**	**138.71**

Table 10: Summary of Pharmacokinetic Parameters of Test Product-T and Reference Product –R

PK Parameter	N	Untransformed Data (Mean ± SD)	
		Test Product (T)	Reference product (R)
C_{max} (ng/mL)	30	878.3199 ± 126.7126	856.8452 ± 146.3876
AUC_{0-t} (ng.hr/mL)	30	41208.6602 ± 12251.5548	39707.4398 ± 13022.8598
$AUC_{0-\infty}$ (ng.hr/mL)	30	46252.0556 ± 19741.4433	43320.0612 ± 16520.8670
*t_{max} (hr)	30	4.98 (3.00-10.00)	4.00 (3.00-12.00)
K_{el} (hr^{-1})	30	0.0219 ± 0.0066	0.0216 ± 0.0078
$t_{1/2}$ (hr)	30	35.2564 ± 13.4131	36.5769 ± 14.9671
K_{el_Lower} (hr)	30	39.1053 ± 34.8231	41.1903 ± 34.5327
K_{el_upper} (hr)	30	139.5280 ± 13.1087	139.4313 ± 13.1749
$AUC_{\_\%Extrap\_obs}$ (%)	30	7.7471 ± 8.6547	6.9097 ± 5.4238

* Expressed in terms of median (range)

Pharmacokinetic Linear and Semi-logarithmic scattered Plots of Individual Plasma Concentration vs. Time for lamotrigine by treatment (N=30)

Figure 2

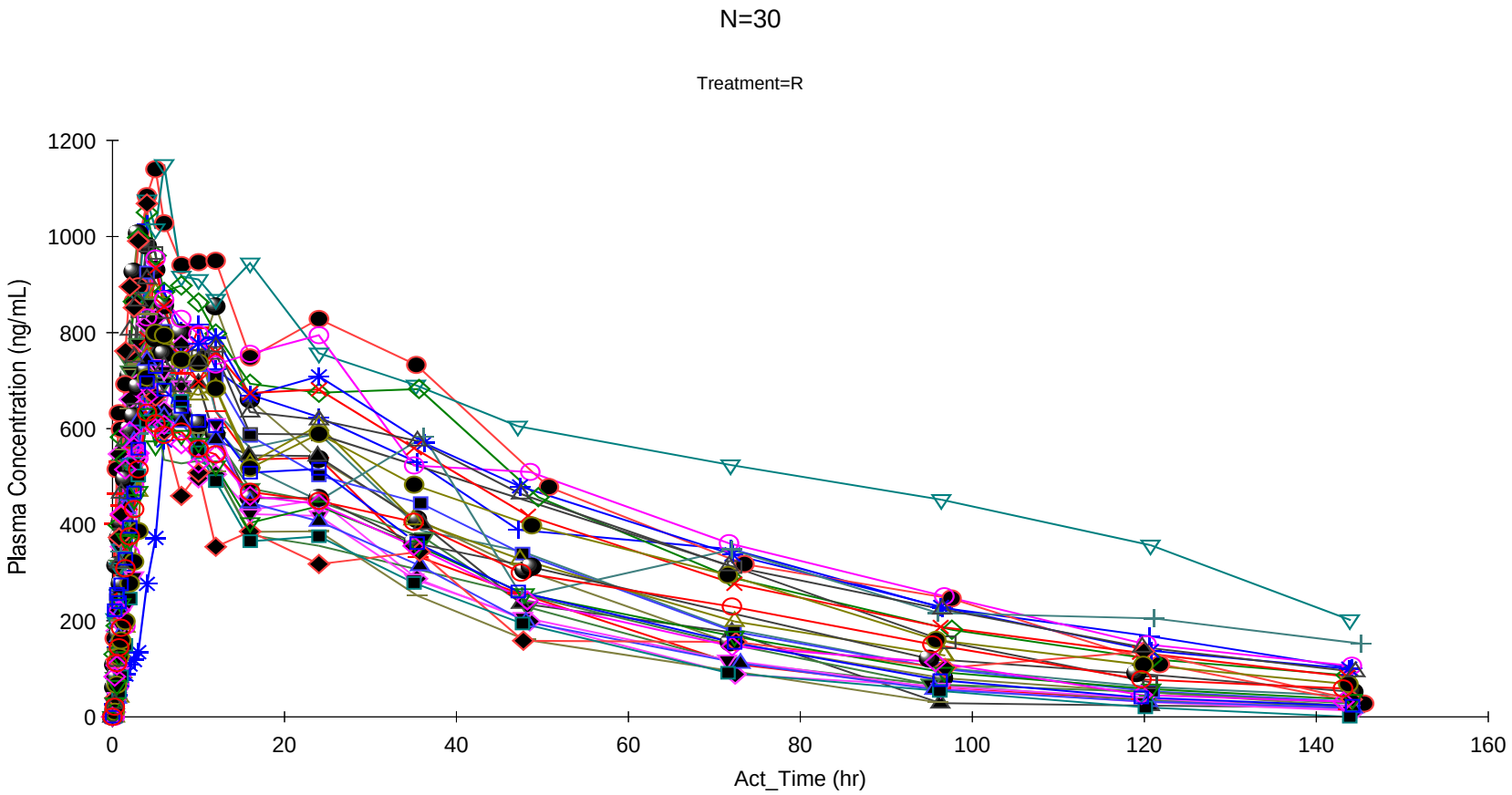


Figure 3

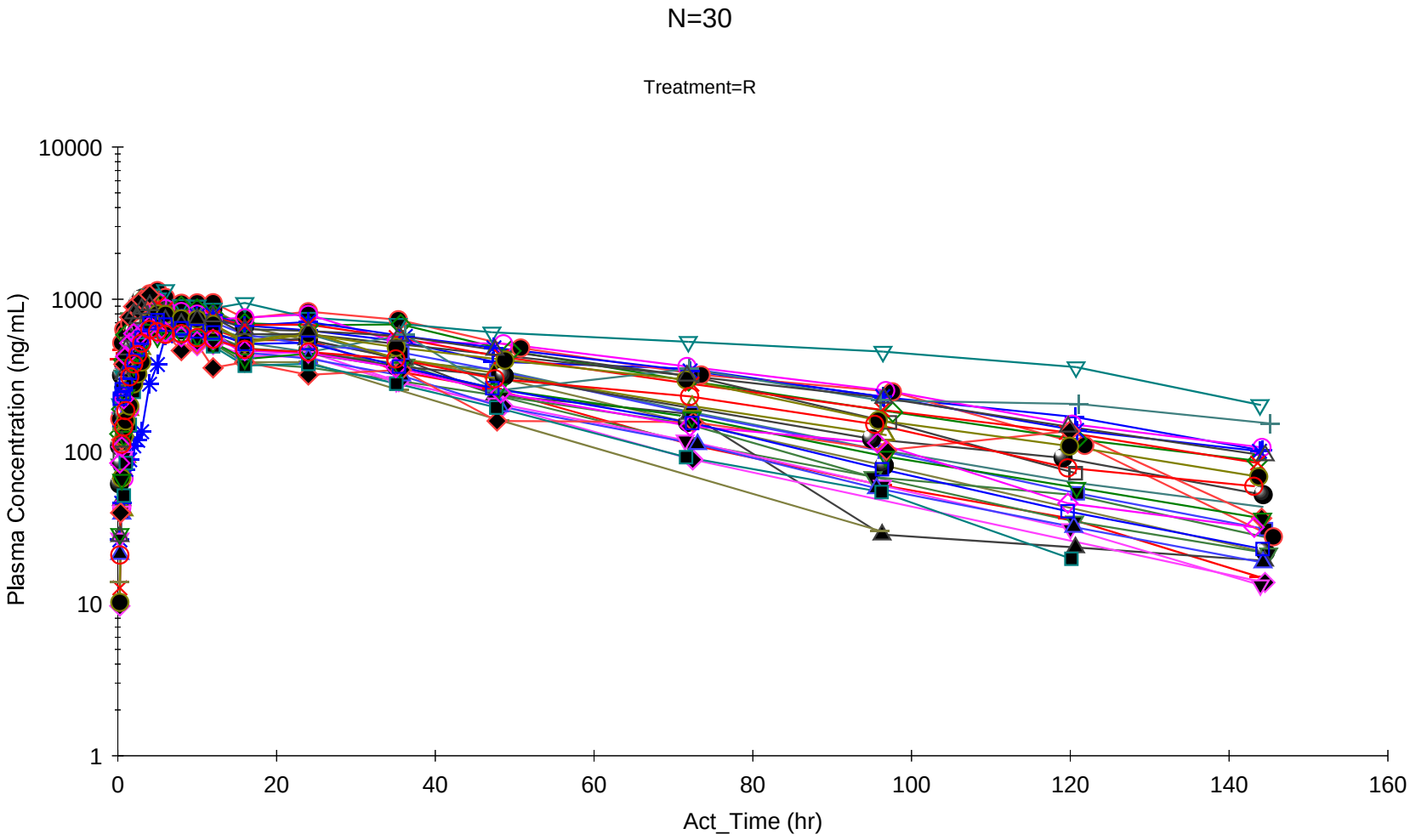

N=30
Treatment=R
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
20
40
60
80
100
120
140
160
Act_Time (hr)

Figure 4

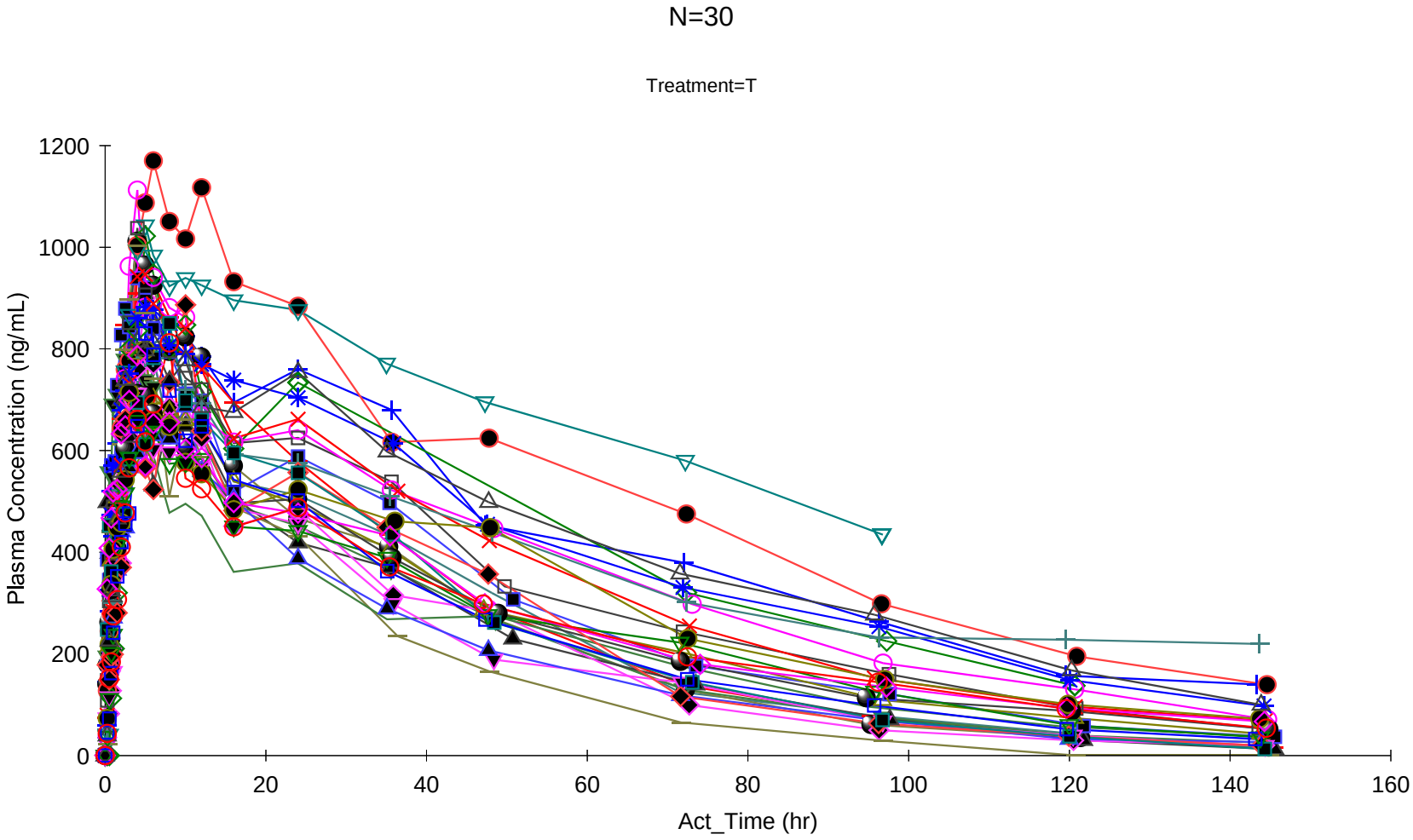
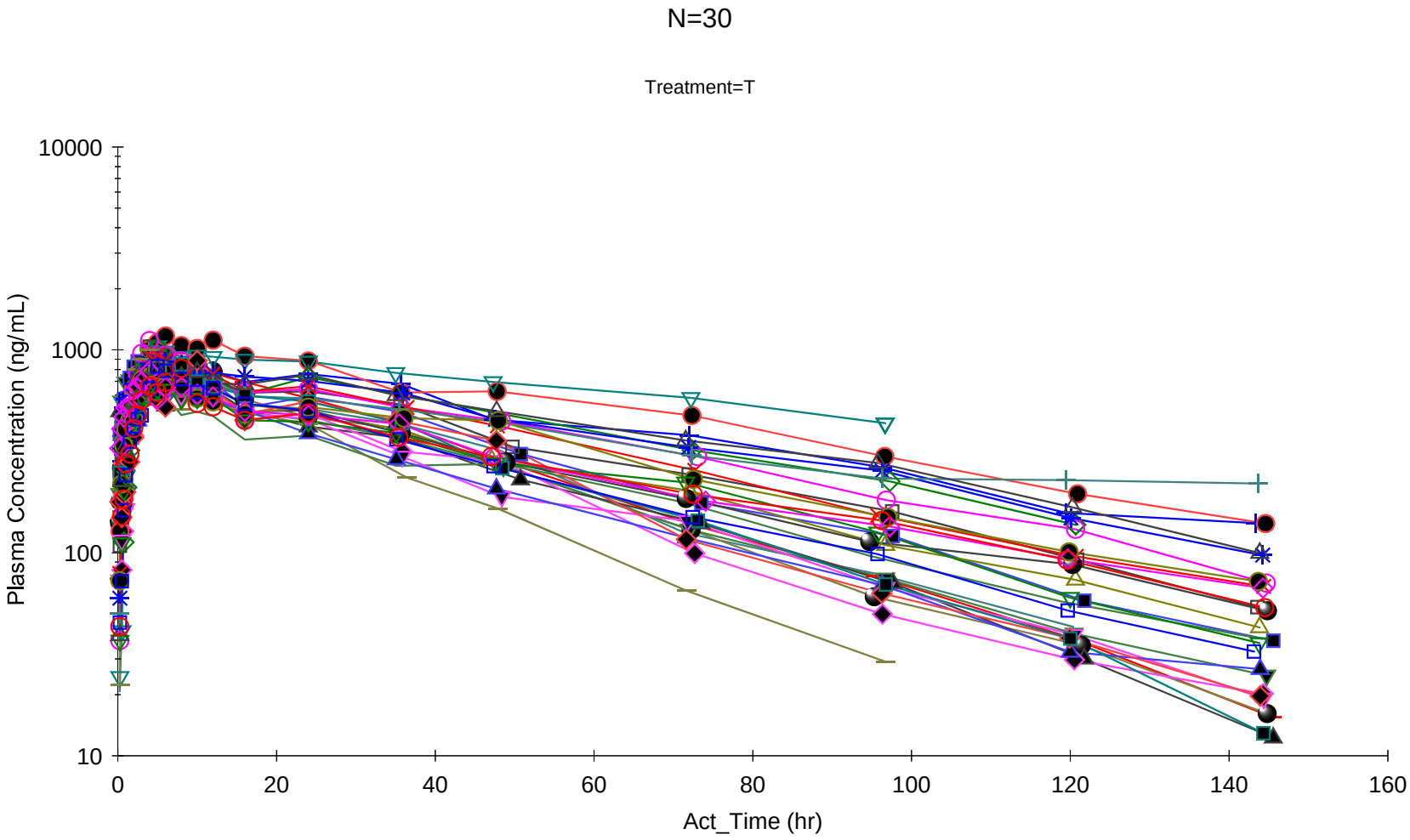

N=30
Treatment=T
Plasma Concentration (ng/mL)
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
140
160
Act_Time (hr)

Figure 5


N=30
Treatment=T
Plasma Concentration (ng/mL)
10000
1000
100
10
0
20
40
60
80
100
120
140
160
Act_Time (hr)

Pharmacokinetic Linear and Semi-logarithmic Plots of Mean Plasma Concentration vs Time for lamotrigine (N=30)
Figure 6

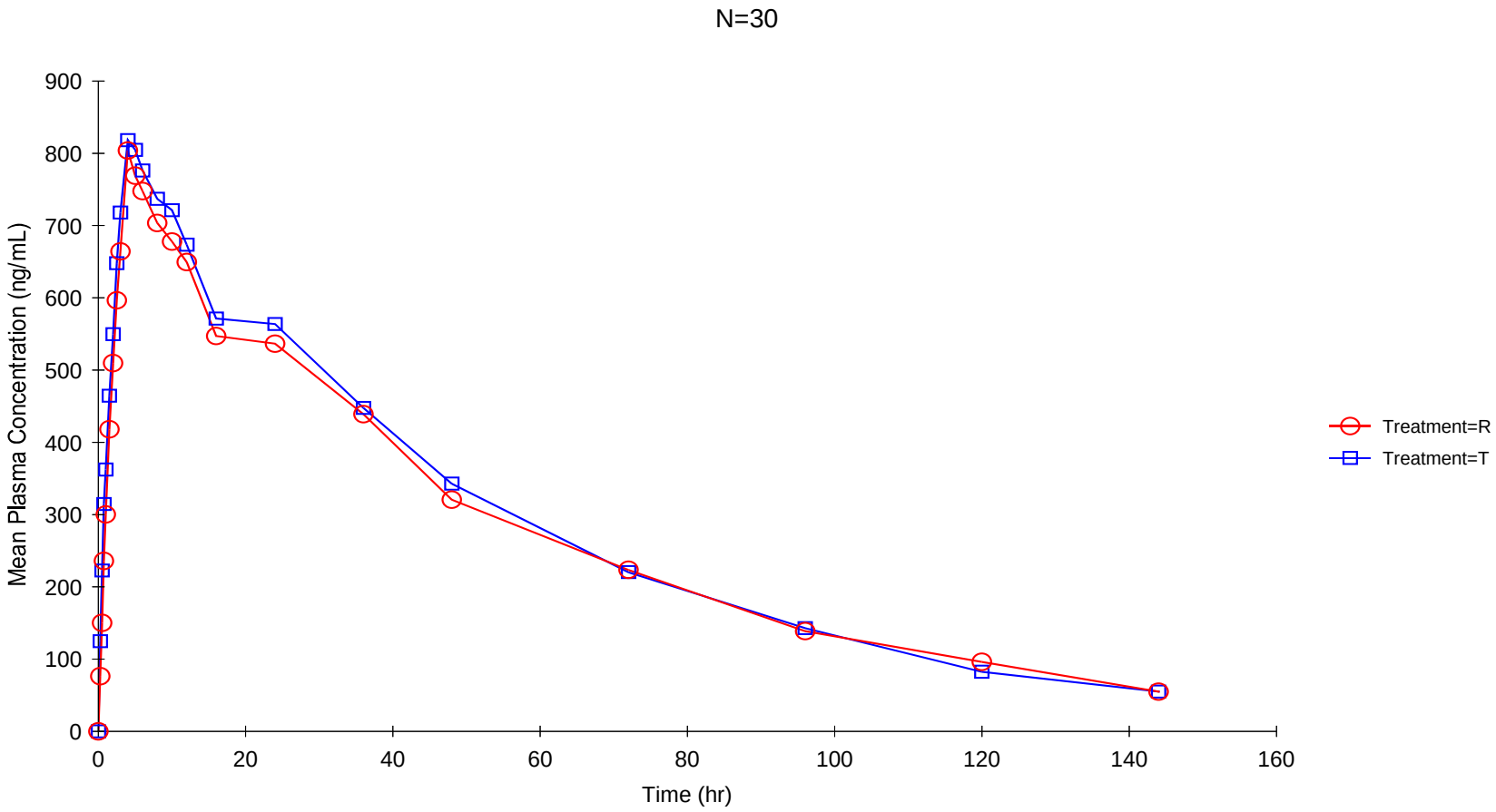
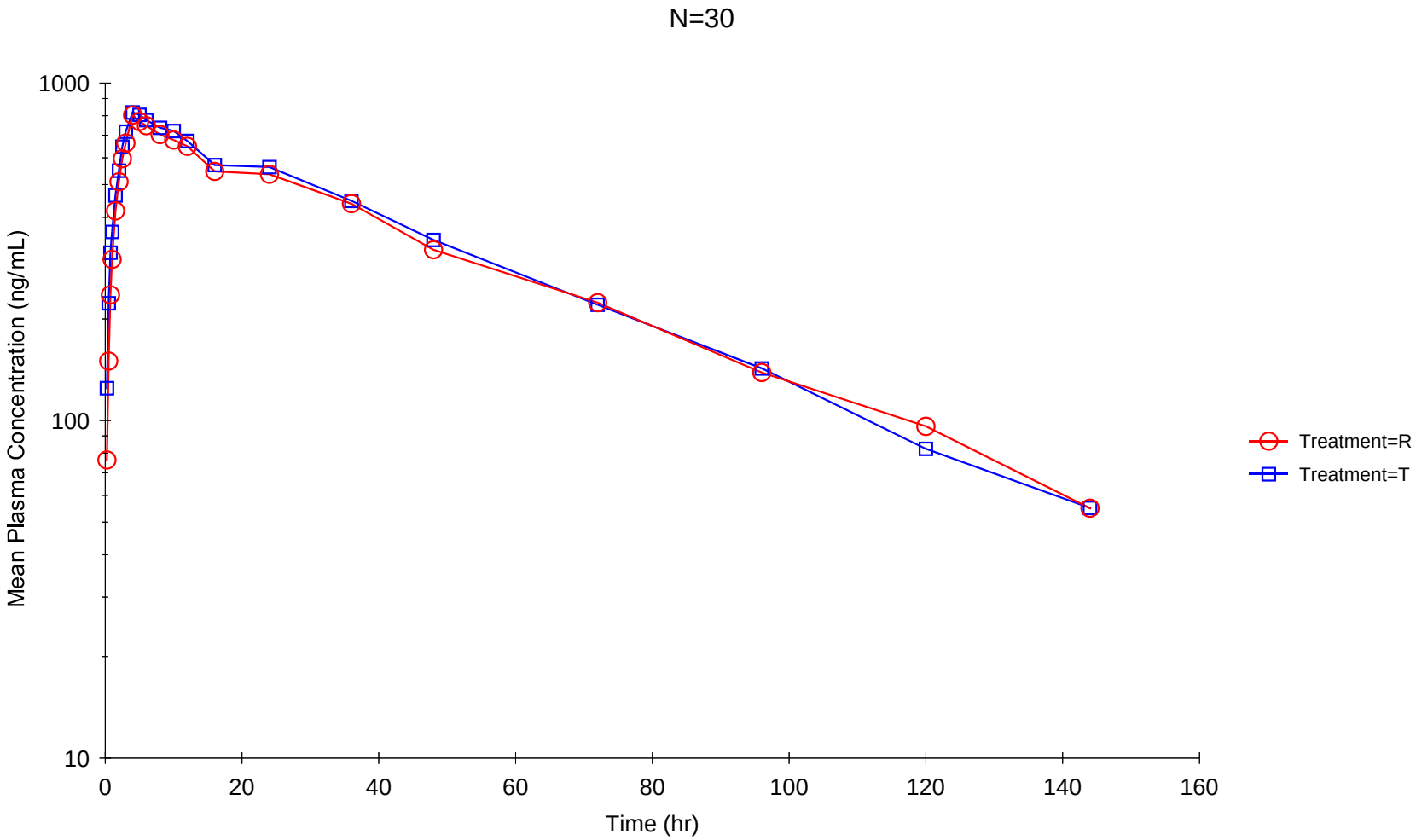


Figure 7


N=30
1000
100
10
Mean Plasma Concentration (ng/mL)
0
20
40
60
80
100
120
140
160
Time (hr)
Treatment=R
Treatment=T

Statistical Analysis

The individual pharmacokinetic parameters for each subject according to treatment are given in table 8 and table 9. For Lamotrigine, analysis of variance (ANOVA) was performed on the Ln-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using mixed procedure of SAS® (version 9.2) software. The analysis of variance model included sequence, period and treatments as fixed effect and the subjects nested within the sequence as the error term at 5% level of the significance. For all analysis, effects were considered statistically significant if the probability (p-value) associated with 'F' was less than 0.05. Based on comparisons of the test and reference product for Ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ data, the ratio of the least square mean was calculated, as well as the 90% confidence intervals for Ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and also the intra-subject CV % was determined.

Peak or maximal plasma concentration (C_{max}):

This parameter was calculated for each subject with respect to treatment and the results are presented in mean values (± SD) of C_{max} for test product (T) was 878.3199 ± 126.7126 ng/mL and for reference product (R) was 856.8452 ± 146.3876 ng.hr/mL.

Area under the concentration-time curve from time zero to t (AUC_{0-t}):

This parameter was calculated for each subject with respect to treatment and the results are presented in mean values (± SD) of AUC_{0-t} for test product (T) was 41208.6602 ± 12251.5548 ng.hr/mL and for reference product (R) was 39707.4398 ± 13022.8598 ng.hr/mL.

Area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$):

This parameter was calculated for each subject with respect to treatment and the results are presented in mean values (±SD) for $AUC_{0-\infty}$ for test product (T) was 46252.0556 ± 19741.4433 ng.hr/mL and for reference product (R) was 43320.0612 ± 16520.8670 ng.hr/mL.

The ANOVA was performed on the Ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ parameters. The least-square mean ratio, the 90% confidence intervals and intra-

subjects CVs were also determined for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. These results are summarized in the following Table 11.

Table 11: Statistical Results of Test Product-T versus Reference Product-R for Lamotrigine

PK Parameter	Anti Log of Least Square Mean		(T/R) Ratio %	90% Confidence Intervals	Intra subject CV (%)
	Test Product (T)	Reference Product (R)			
C_{max} (ng/mL)	869.6279	844.8876	102.93 %	99.78 % to 106.17 %	7.07 %
AUC_{0-t} (ng.hr/mL)	39619.839	37863.430	104.64 %	101.11 % to 108.29 %	7.83 %
$AUC_{0-\infty}$ (ng.hr/mL)	43173.858	40745.005	105.96 %	102.05 % to 110.03 %	8.59 %

Statistical / Analytical Issues

There were no statistical/analytical issues observed in the study.

Adjustments of Covariates

No adjustment for covariates was made.

Pharmacokinetic Conclusions

Based on the results obtained, Lamotrigine tablets 50 mg manufactured by Edict Pharmaceuticals, Chennai, India and LAMICTAL® ODT™ orally disintegrating tablets 50 mg tablets, manufactured by GlaxoSmithKline, Research Triangle Park, NC 27709 following a single dose of 50 mg are found to be bioequivalent in healthy, adult, human subjects under fed conditions.

6.2 SAFETY EVALUATION

Extent of Exposure

Subjects were administered a single oral dose of Lamotrigine 50 mg tablet [test or reference, as per randomization schedule on two occasions with a washout period of 14 days between dosing of each period. All the 30 subjects were exposed to both test and reference treatments.

Adverse Events (AE's)

Brief Summary of Adverse Events

The details of the AEs including the name of the event, intensity, onset and resolution date, outcome, relation to the study product and action taken to manage the events are presented in table 12.

Analysis of Adverse Events

During the conduct of the study, there were totally two adverse events noted. Both the adverse events were mild and there was a possibility of the adverse event being related to the drug in S02. Subject no. S02 reported adverse event of Nausea after dosing of the test product in period I and the adverse event was resolved without any sequelae on the same day and the subject was not withdrawn from the study. S03 reported adverse event of Fever and Loss of appetite after dosing of the test product in period II and the subject was treated with Combiflam (Ibuprofen + Paracetamol) 400mg+500mg (one tablet) and the adverse event was resolved without any sequelae on the next day and the possibility of the adverse event being related to the drug is None/Doubtful. The above said subjects were not withdrawn from the study. There were no adverse events recorded during post study evaluation.

Deaths, Other Serious Adverse Events, and other Significant Adverse Events

There were no deaths, SAE or significant adverse events noted in this study.

Safety Conclusions

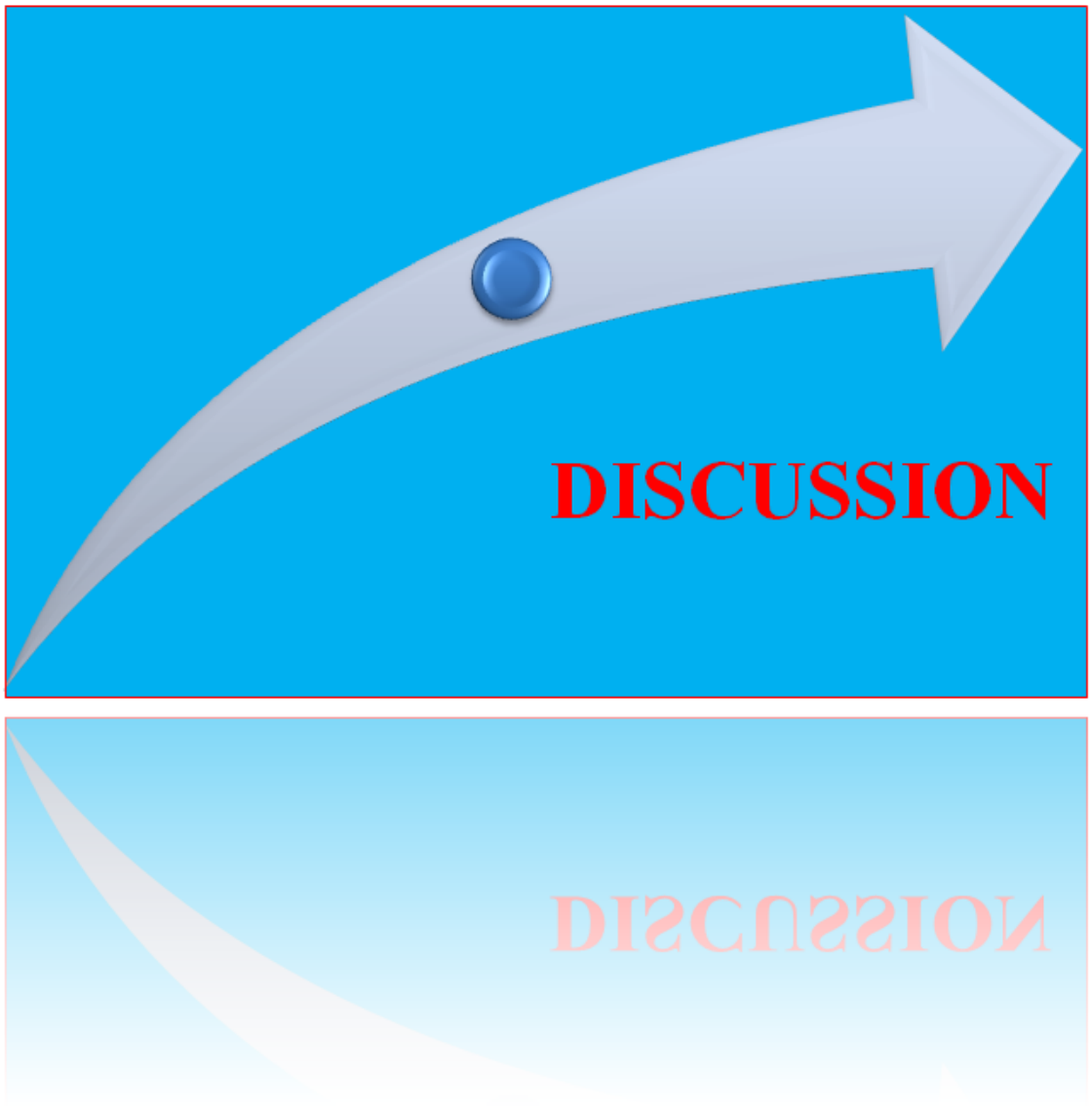
The incidence of adverse event reported after administration of test and reference products were given in table 12. Safety was evaluated from screening till completion of study through clinical examination, lab evaluation and vital sign assessment. Two adverse events were reported during in-house confinement. There were no adverse events reported during post study evaluation. There were no serious adverse event(s) reported during the study. Thus it can be reasonably concluded that both the test and reference products were comparable at the selected dose level.

Table 12: Adverse events

Subject No.	Name of the Event	Treatment	Description		Onset Date	Resolution Date	Action Taken	Severity	Outcome	Relationship to study Products
			Pre-study value	Post-study value						
S02	Nausea	T	N/AP	N/AP	20 Dec 13	21 Dec 13	Nil	Mild	Resolved	Possible
S03	Fever, Loss of appetite	T	N/AP	N/AP	08 Jan 14	09 Jan 14	Treated with one tablet of Combiflam (Ibuprofen and Paracetamol, 400 mg + 500 mg)	Mild	Resolved	None/Doubtful

Test Product (T): Lamotrigine tablets 50 mg manufactured by Edict Pharmaceuticals, Chennai, India.

Reference Product (R): LAMICTAL® ODT™ (Lamotrigine) Orally Disintegrating Tablets 50 mg of GlaxoSmithKline,Research Triangle Park, NC2770Listing of Deaths, other Serious and Significant Adverse Events

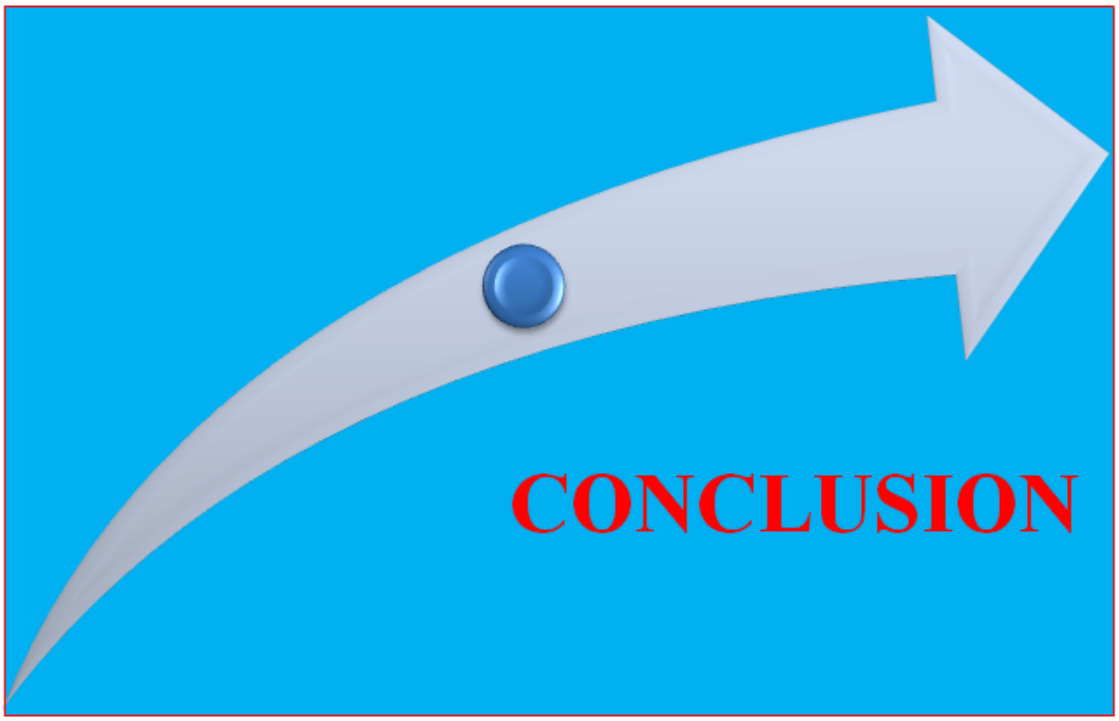

DISCUSSION

7. DISCUSSION

The main objectives of this study was to evaluate the relative bioavailability of Lamotrigine of Edict Pharmaceuticals with that LAMICTAL® ODT™ (Lamotrigine) orally disintegrating tablets 50 mg of GlaxoSmithKline, Research Triangle Park, NC27709 in 32 healthy, human, adult subjects under fed conditions and to monitor the safety of subjects.

32 subjects in the age group of 18 to 42 years who met the eligibility criteria were enrolled into the study and all the enrolled subjects were completed the study, except S16 and S30. The study was conducted over a period of 22days with a washout period of 14 days. Vital signs were comparable throughout the study. Only S16 and S30 reported mild adverse event during the course of the study, but resolved without any sequelae. Thus it can be reasonably concluded that the investigational products were safe and well tolerated at the selected dose level in the human subjects.

The pharmacokinetic and statistical analyses were performed on data from 30 subjects. The results of the pharmacokinetic analysis of Lamotrigine with the test product were comparable to the reference product. Analysis of variance for Ln-transformed pharmacokinetic parameters revealed that there was no significant effect of variation due to sequence for all the primary pharmacokinetic parameters with the p-values 0.6084, 0.4531 and 0.3321 for $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty.}$ C_{max} is significant for period with the p-value 0.0243 and insignificant for treatment with the p-value 0.1247. AUC_{0-t} is significant for treatment and insignificant for period with the p-values 0.0327 and 0.6889. $AUC_{0-\infty}$ is significant for treatment and insignificant for period with the p-values 0.0142 and 0.7834 respectively.

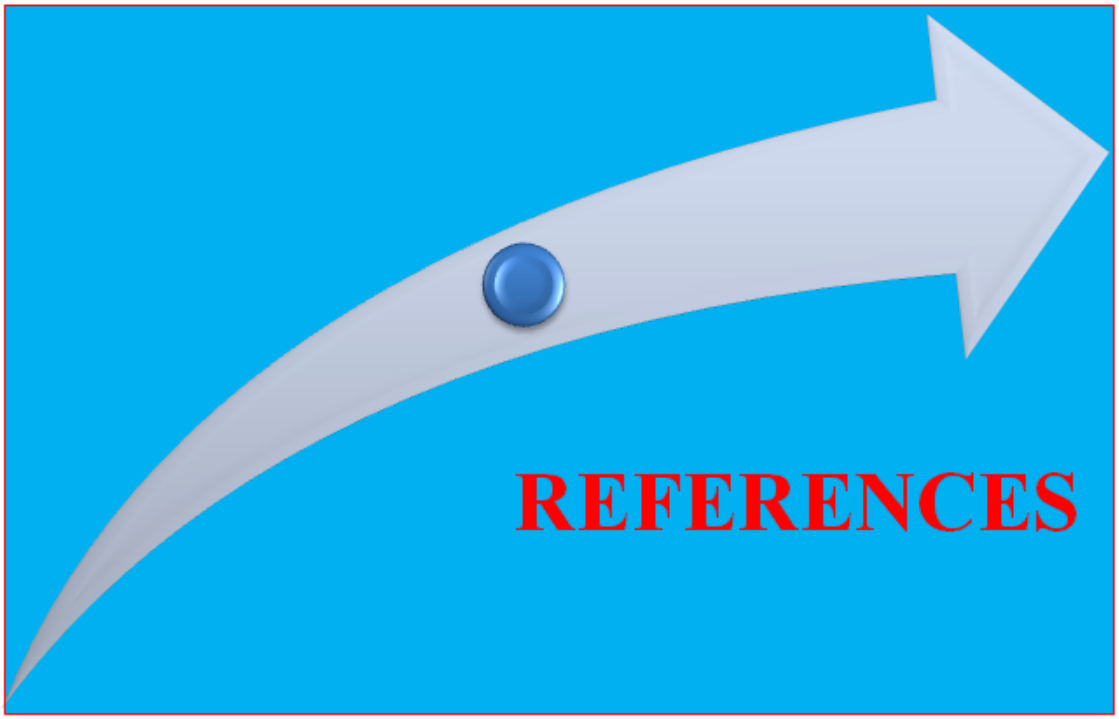

CONCLUSION

8. CONCLUSION

The main objective of bioequivalence studies is to assure the efficacy and safety of generic formulations. Therefore, two formulations of the same drug are considered to be bioequivalent and ergo therapeutically equivalent if they exhibit a comparable extent and rate of absorption, when they are administered in the same molar dose and under similar experimental conditions. The study procedure was followed as per the GCP, ICMR, and thics committee guidelines to ensure the wellbeing of the study subjects. The duration of the study was followed as 22 days with the wash out period of 14 days to compare the reference and test products of Lamotrigine 20 mg tablets.

The 90% confidence interval of the least square mean of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were (99.78 % to 106.17 %), (101.11 % to 108.29 %) and (102.05 % to 110.03 %), respectively, within the limit of 80.00 % and 125.00 %. Two adverse events were reported during in-house confinement for the test product. There were no adverse events reported during post study evaluation and no serious adverse events reported during the study. It can be reasonably concluded that both the test and reference products were comparable for safety at the selected dose level.

Based on the results obtained in this study, test product Lamotrigine Orally Disintegrating 50 mg Tablets and reference product LAMICTAL® ODT™ (Lamotrigine) Orally Disintegrating 50 mg Tablets are found to be bioequivalent and well tolearated in healthy, adult, human subjects under fed conditions.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TO WHOMEVER IT MAY CONCERN

This is to certify that V.Saravanan, Second year M. Pharmacy student from Mohamed Sathak A.J. College of Pharmacy, Sholinganallur, Chennai – 600119 has completed his project entitled "An open-label, balanced, randomized, two-treatment, two-period, two sequence, single dose, two-way crossover, bioequivalence study of Lamotrigine 50 mg in healthy, adult, human subjects under fed conditions" as a part of his M. Pharmacy curriculum in our organization under my guidance and supervision during the academic year 2013-14.

K. Azagesan 13 Feb 14.

(K. Azagesan)

Department of clinical operations-Lead

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